Long-acting reversible contraception: the effective and appropriate use of long-acting reversible contraception

National Collaborating Centre for Women's and Children's Health

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2nd draft guideline

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Association of British Health-Care Industries
Association of Surgeons of Great Britain and Ireland
Association of the British Pharmaceuticals Industry, (ABPI)
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British Association for Counselling and Psychotherapy
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Sheffield Teaching Hospitals NHS Trust
South & Central Huddersfield Primary Care Trust
South Birmingham Primary Care Trust
SSL International plc
Tameside and Glossop Acute Services NHS Trust
The Royal Society of Medicine
The Royal West Sussex Trust
The Survivors Trust
Trafford Primary Care Trusts
University College London Hospitals NHS Trust
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Abbreviations

AIDS	Acquired immunodeficiency syndrome
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BTB	Breakthrough bleeding
CHC	Combined hormonal contraceptive
CI	Confidence Interval
COC	Combined oral contraceptive
CVD	Cardiovasuclar disease
DFFP	Diploma of the Faculty of Family Planning and Reproductive Health Care
DH	Department of Health
DMPA	Depot medroxyprogesterone acetate
*e*MC	Electronic Medicines Compendium
ENG	Etonogestrel
FPC	Family Planning Clinic
FFPRHC	Faculty of Family Planning and Reproductive Health Care
GDG	Guideline Development Group
GP	General Practitioner
GPP	Good Practice Point
GRP	Guideline Review Panel
GU	Genito-urinary
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IUD	Intrauterine device
IUS	Intrauterine system
LARC	Long acting reversible contraception
LDL	Low Density Lipoprotein
LNG	Levonorgestrel

LoC	Letter of Competence
LSHTM	London School of Hygiene & Tropical Medcine
MBL	Menstrual blood loss
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MPA	Medroxyprogesterone acetate
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NET-EN	Norethisterone enantate
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NMC	Nursing and Midwifery Council
NSAID	Non-steroidal anti-inflammatory drugs
OC	Oral contraceptive pill
OR	Odds ratio
PCT	Primary Care Trust
PID	Pelvic inflammatory disease
POC	Progestogen-only oral contraceptive
POICs	Progestogen-only injectable contraceptives
POIUS	Progestogen-only intrauterine system
POSDIs	Progestogen-only subdermal implants
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation
STI	Sexually transmitted infections
STIF	Sexually transmitted infections foundation course
TOP	Termination of pregnancy
TTP	Time to pregnancy
UKSPR	UK Selected Practice Recommendations for Contraceptive Use
VTE	Venous thromboembolism
WHO	World Health Organization
WHO-MEC	World Health Organization Medical Eligibility Criteria for Contraceptive Use

WHO-SPR	World Health Organization Selected Practice Recommendations for Contraceptive Use

Glossary of terms

Amenorrhoea Absence of menstrual bleeding

Bias Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it does not. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, for example, in the randomization, collection, analysis, interpretation, publication or review of research data.

Blinding or masking The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also double blind study.

Case–control study A study that starts with the identification of a group of individuals sharing the same characteristics (for example, people with a particular disease) and a suitable comparison (control) group (for example, people without the disease). All subjects are then assessed with respect to things that happened to them in the past, for example, things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.

Case report (or case study) Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.

Case series Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no

comparison (control) group of patients.

Clinical trial A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.

Cohort A group of people sharing some common characteristic (for example, patients with the same disease), followed up in a research study for a specified period of time.

Cohort study An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, for example, comparing mortality between one group that received a specific treatment and one group that did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Confidence interval A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that is consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence

intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which there is 95% confidence that the true effect lies.

Control group A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Controlled clinical trial A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A controlled clinical trial where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.

Cost-Effectiveness Analysis A type of economic evaluation where outcomes are expressed in natural units (e.g. number of cases cured, number of lives saved, etc)

Crossover study design A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.

Cross-sectional study The observation of a defined set of people at a single

point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.)

Decision-Analytic Model A mathematical simulation of the real world, where cost and outcome data derived from various sources are incorporated, resulting in the estimation of the relative cost-effectiveness between two or more interventions; it enables economic evaluation of alternative courses of action, therefore contributing to decision-making.

Dominance A possible result of comparison between two alternatives in economic evaluation; one intervention is said to dominate its comparator when it is both more effective and less costly.

Double blind study A study in which neither the subject (patient) nor the observer (investigator or clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.

Dysmenorrhoea Painful menstrual bleeding

Economic Evaluation The comparative analysis between two or more interventions, in terms of both their costs and outcomes.

Evidence-based clinical practice Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.

Evidence table A table summarising the results of a collection of studies which, taken together, represent the body of evidence supporting a particular recommendation or series of recommendations in a guideline.

Exclusion criteria See selection criteria.

Experimental study A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease, where the conditions of testing are to some extent under the control of the investigator. Controlled clinical trial and randomised controlled trial are examples of experimental studies.

Extrapolation The projection or extension of directly established knowledge to an area not presently open to observation on the basis of known data.

Fraser Guidelines A set of criteria which must be applied when medical practitioners are offering contraceptive services to under 16's without parental knowledge or permission. These guidelines stem from the legal challenge by Victoria Gillick in the early 1980s to medical practitioners right to provide children under 16 years of age treatment or contraceptive services without parental permission. On occasion practitioners may refer to assessing whether a young person is ***Gillick competent***.

Gillick competence See ***Fraser Guidelines***.

Gold standard A method, procedure or measurement that is widely accepted as being the best available.

Hazard ratio In survival analysis, a summary of the difference between two survival curves, representing the reduction in the risk of death on treatment compared to control, over the period of follow-up.

Health economics A field of conventional economics which examines the benefits of healthcare interventions (for example, medicines) compared with their financial costs.

Heterogeneity Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment

from separate studies seem to be very different, in terms of the size of treatment effects, or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of patient populations, outcome measures, definition of variables or duration of follow-up.

Homogeneity This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.

Incidence The rate of occurrence or influence; *especially* the rate of occurrence of new cases of a particular disease in a population being studied.

Inclusion criteria See selection criteria.

Incremental Cost-Effectiveness Ratio A method of presentation of results of an economic evaluation; it expresses the additional (incremental) cost incurred for an additional unit of benefit gained, by adopting an intervention over its comparator.

Intervention Healthcare action intended to benefit the patient, for example, With drug treatment, surgical procedure or psychological therapy.

Kaplan-Meier method The Kaplan-Meier method is a nonparametric technique for estimating time-related events (the survivourship function). Ordinarily it is used to analyse death as an outcome. It may be used effectively to analyse time to an endpoint, such as remission.

Longitudinal study A study of the same group of people at more than one point in time. (This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time.)

Masking See blinding.

Menarche The beginning of the menstrual function, particularly the first menstrual period of a female.

Menopause The period of natural cessation of menstruation, usually occurring between the ages of 45 and 50 years.

Menorrhagia Excessive or prolonged menstrual bleeding.

Metromenorrhagia Uterine bleeding between menstrual periods and increased flow of bleeding during menstrual periods.

Meta-analysis Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, for example, because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also systematic review and heterogeneity.

Non-experimental study A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.

Nulliparity Having never given birth to a viable infant.

Observational study In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (for example, whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.

Odds ratio Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of one between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also relative risk and risk ratio.

Oligomenorrhoea Reduction in the frequency of menstrual bleeding.

One level service Minimum level of provision within primary care sexual health services.

Osteopenia Decreased calcification or density of bone.

Osteoporosis A reduction in the amount of bone mass that can lead to fractures after minimal trauma.

Peer review Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional, patient and carer representatives.

Peri-menopausal The time leading up to menopause when oestrogen levels begin to drop.

Placebo Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial, which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants and investigators are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.

Placebo effect A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.

Post partum Occuring in or being the period following childbirth.

Power See statistical power.

Premenstrual syndrome Symptoms manifested by some women prior to menstruation including irritability, insomnia, fatigue, headache and abdominal pain.

Prevalence The number of cases of disease or other eventualities which occur in a population at or during a given time.

Prospective study A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.

P value If a study is done to compare two treatments then the p value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the p value was 0.03. What this means is that, if there really was no difference between treatments, there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of p is below 0.05 (that is, less than 5%) the result is seen as statistically significant. Where the value of p is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the confidence interval.

Qualitative research Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, for example, a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.

Quantitative research Research that generates numerical data or data that can be converted into numbers, for example, clinical trials or the National Census, which counts people and households.

Random allocation or randomisation A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.

Randomised controlled trial A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)

Relative risk A summary measure which represents the ratio of the risk of a given event or outcome (for example, an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk'

of the event is the same in the two groups the relative risk is one. In a study comparing two treatments, a relative risk of two would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.

Reliability Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession and if their assessments tend to agree then the method of assessment is said to be reliable.

Retrospective study A retrospective study deals with the present and past and does not involve studying future events. This contrasts with studies that are prospective.

Risk ratio Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym for risk ratio.

Sample A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.

Screening The presumptive identification of an unrecognised disease or defect by means of tests, examinations or other procedures that can be applied rapidly. Screening tests differentiate apparently well people who may have a disease from those who probably do not. A screening test is not intended to be diagnostic but should be sufficiently sensitive and specific to reduce the proportion of false results, positive or negative, to acceptable

levels. People with positive or suspicious findings must be referred to the appropriate healthcare provider for diagnosis and necessary treatment.

Selection criteria Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Sensitivity analysis A technique used in economic evaluation, in order to test the robustness of the results under the uncertainty/imprecision in the estimates of costs and outcomes, or under methodological controversy.

Statistical power The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a p value of less than 5% in a statistical test (that is, a statistically significant treatment effect) if there really was an important difference (for example, 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also p value.

Sterilisation – female Surgical obstruction of the fallopian tubes.

Sterilisation – male Surgical contraceptive method, whereby the vas deferens undergoes bi-lateral ligation or interruption.

Systematic review A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.

Validity Assessment of how well a tool or instrument measures what it is intended to measure.

Variable A measurement that can vary within a study, for example, the age of

participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature that can be assessed or measured.

1 Introduction

Contraception can be broadly divided into two large categories, hormonal and non-hormonal. There are two categories of hormonal contraception, combined and progestogen only. Long acting reversible contraception (LARC) is defined in this guideline as methods that require administering less than once per cycle or month.

Included in the category of LARC are the copper intrauterine device (non-hormonal) and three progestogen-only methods of contraception (intrauterine system, injectables and the implants).

In 2003/4, about 8% of women aged 16-49 years in the UK used long acting reversible contraceptives as a method of contraception.[1][EL=3]

1.1 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[2] The guideline has been developed with the aim of providing guidance on LARC. The effectiveness of barrier and oral contraceptive pills is dependent on their correct and consistent use. By contrast, long-acting reversible methods have effectiveness that does not depend on daily compliance. Currently there is a very low uptake of long-acting reversible contraception (around 8% of contraceptive usage in 2003/4[1]). A number of factors contribute to this. Issues for providers include the initial cost, which may be thought of as too high particularly if the methods may not be used or required for the intended duration, the need for specific clinical skills (including awareness of current best practice, insertion practice and ability to give information or advice on the methods available) and facilities. Expert clinical opinion is that long-acting reversible contraceptive methods may have a wider role and an increase in their use could help to

reduce unintended pregnancy. The current very low uptake of long-acting reversible contraception suggests that health professionals need better guidance and training so that they can help women to make an informed choice from a full range of contraceptive methods. Enabling women to make an informed choice about long-acting reversible contraception and addressing consumer preferences is an important objective of this guideline.

There are no current formal professional or NHS guidelines covering this topic that are widely used or tailored to cover UK practice. The guideline offers best practice advice for all women of reproductive age who may wish to regulate their fertility through the use of long-acting reversible contraceptive methods and specific issues for the use of these methods in women during the menarche and before the menopause. The guideline also identifies specific issues that may be relevant to particular groups, including women with HIV, learning disabilities, physical disability and under 16s.

1.2 Areas outside the remit of the guideline

The guideline does not include any contraception for men because there are currently no long-acting reversible methods. The guideline does not cover methods of contraception that are intended to result in permanent sterilisation. Contraceptive methods that are related to coitus or that require frequent (more than once per cycle (month) for women) repeat administration – for example, the combined oral contraceptive pill or progestogen-only pills are also not included. Post-coital or emergency contraceptive methods including IUD insertion for that use are also not covered. The use of these technologies for non-contraceptive reasons (such as heavy menstrual bleeding or hormone replacement therapy) are outside the scope of this guideline.

1.3 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the National Health Service in England and Wales. In particular, the guideline will cover the

necessary elements of clinical care for provision of long-acting reversible methods of contraception in general practice, community contraceptive clinics, sexual health clinics and hospital services.

1.4 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH).

Membership included:

- Two consumers
- Two general practitioners
- Two family planning nurses
- Three specialist family planning doctors
- One genitourinary medicine physician.

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval and appraisal of the evidence, and wrote successive drafts of the guideline.

All GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, shareholdings, fellowships, and support from the healthcare industry in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

1.5 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including A strategic framework for sexual health in Wales (January 2000)[3]. The national strategy for sexual health and HIV (in

England; July 2001)[4], and the subsequent implementation plan (June 2002)[5]. Improving access to contraception, and to the range of methods available as an integral part of broader sexual health services, are essential elements of achieving this aim.

1.6 Guideline methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at http://www.nice.org.uk)[6].

1.7 Literature search strategy

The aim of the literature review was to identify and synthesise relevant published evidence. However, evidence submitted by stakeholder organisations was considered and, if relevant to the clinical questions and of equivalent or better quality than evidence identified in the literature searches, was also included.

Relevant guidelines produced by other development groups were identified using Internet resources, including the National Guideline Clearinghouse, Scottish Intercollegiate Guideline Network (SIGN) and Turning Research into Practice (TRIP). The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Evidence to answer the clinical questions formulated and agreed by the GDG was identified using biomedical databases via the OVID platform. Searches were performed using relevant medical subject headings and free-text terms. No language restrictions were applied to the searches. Both generic and specially developed search filters were employed when necessary. Databases searched were MEDLINE (1966 onwards), EMBASE (1980 onwards),

Cochrane Central Register of Controlled Trials (4th Quarter 2004), Cochrane Database of Systematic Reviews (4th Quarter 2004), Database of Abstracts of Review of Effects (4th Quarter 2004), and Cumulative Index to Nursing & Allied Health Literature (1982 onwards). POPLINE®, a specialist reproduction database maintained by Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs, was also utilised.

Searches to identify economic studies were undertaken using the above databases, as well as the Health Economic Evaluations Database and the National Health Service Economic Evaluations Database. Further details on the systematic review of the economic literature are provided in chapter 8.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the biomedical databases was not carried out.

A preliminary scrutiny of titles and abstracts was undertaken and full copies of publications that addressed the clinical questions were obtained. Following a critical appraisal of each publication, studies that did not report relevant outcomes or were not relevant to a particular clinical question were excluded. Searches were rerun at the end of the guideline development process, thereby including evidence published and included in the literature databases up to 1 February 2005. Any evidence published after this date was not considered for inclusion. This date should be considered for the starting point for searching for new evidence for future updates to this guideline.

Further details of literature searches can be obtained from the NCC-WCH.

1.8 Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established

guides[7-13] and classified using the established hierarchical system shown in Table 1.1.[13] This system reflects the susceptibility to bias that is inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each paper receives a quality rating coded as '++', '+' or '–'. For issues of therapy or treatment, the highest possible level of evidence (EL) is a well-conducted systematic review or meta-analysis of RCTs [EL=1++] or an individual RCT [EL=1+]. Studies of poor quality are rated as '–'. Usually, studies rated as '–' should not be used as a basis for making a recommendation, but they can be used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study [EL=2-].

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not included. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was used.

In contraception research, investigators have not attempted to directly measure the true efficacy of a contraceptive method, compared with a control group using no method, because ethical concerns do not permit the withholding of contraception.[14;15] For this guideline, the selection criteria for including studies as source of evidence were based on the comparability of the study population and contraceptive devices to that of the UK, as determined to be appropriate by the guideline development group.

Table 1.1 Levels of evidence for intervention studies[13]

Level	Source of evidence
1++	• High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	• Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	• Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	• High-quality systematic reviews of case–control or cohort studies • High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	• Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	• Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	• Non-analytical studies (for example, case reports, case series)
4	• Expert opinion, formal consensus

Evidence was synthesised qualitatively by summarising the content of identified papers in evidence tables and agreeing brief statements that accurately reflected the evidence. Quantitative synthesis (meta-analysis) was performed where appropriate.

Summary results and data are presented in the guideline text. More detailed

results and data are presented in the accompanying evidence tables. Where possible, dichotomous outcomes are presented as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes are presented as mean differences with 95% CIs or standard deviations (SDs). Meta-analyses based on dichotomous outcomes are presented as pooled ORs with 95% CIs, and meta-analyses based on continuous outcomes are presented as weighted mean differences (WMDs) with 95% CIs.

1.9 Health economics

The aim of the economic input to the guideline was to inform the GDG of potential economic issues related to long-acting reversible contraception. The objective was to assess the relative cost-effectiveness between LARC methods and other contraceptive methods that were considered as relevant comparators by the GDG. For this purpose, a systematic review of the economic literature was undertaken, along with a cost-effectiveness analysis based on a decision-analytic economic model that was developed for this guideline.

The search strategies adopted for the systematic review were designed to identify any economic study related to LARC. Abstracts of all papers identified were reviewed by the health economists and were discarded if they did not relate to the economic questions being considered in the guideline. The relevant papers were retrieved and critically appraised. Potentially relevant references in the bibliographies of the reviewed papers were also identified and reviewed. All papers reviewed were assessed by the health economists against standard quality criteria for economic evaluation. Further details on the systematic review of the economic literature are provided in chapter 8.

The decision analytic model was developed by the health economists with the support of the GDG, who provided guidance on the data needed to populate the model and on the assumptions required to make appropriate comparisons. Full details on the methodology, the structure of the model and the underlying

assumptions, the data used (clinical effectiveness and UK-based cost data), the range of values used in the sensitivity analysis, as well as the full results of the economic analysis are also presented in chapter 8.

A summary of the economic evidence for each LARC method is presented at the end of the relevant chapters.

1.10 Forming and grading recommendations

For each clinical question, recommendations were derived using, and explicitly linked to, the evidence that supported them. Initially guideline recommendations were based on an informal consensus. Consensus was achieved at formal GDG meetings to finalise the agreement of recommendations and audit criteria. Each recommendation was graded according to the level of evidence upon which it was based using the established system shown in Table 1.2.[13] For issues of therapy or treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For issues of prognosis, the best possible level of evidence (a cohort study) would equate to a grade B recommendation. However, this should not be interpreted as an inferior grade of recommendation because it represents the highest level of relevant evidence. Indirect evidence on contraceptive devices not licensed in the UK was extrapolated to form recommendations reflecting a lower grading.

Table 1.2 Classification of recommendations[13]

Class	Evidence
A	• At least one meta-analysis, systematic review, or randomised controlled trial (RCT) that is rated as 1^{++}, and is directly applicable to the target population, **or** • A systematic review of RCTs or a body of evidence that consists principally of studies rated as 1+, is directly applicable to the target population and demonstrates overall consistency of results, **or** • Evidence drawn from a NICE technology appraisal
B	• A body of evidence that includes studies rated as 2^{++}, is directly applicable to the target population and demonstrates overall consistency of results, **or** • Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	• A body of evidence that includes studies rated as 2^{+}, is directly applicable to the target population and demonstrates overall consistency of results, **or** • Extrapolated evidence from studies rated as 2^{++}
D	• Evidence level 3 or 4, **or** • Extrapolated evidence from studies rated as 2^{+}, **or** • Formal consensus
D(GPP)	• A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

1.11 External review

The guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholders the opportunity to comment on the scope of the guideline.

1.12 Outcome measures used in the guideline

For this guideline, the effectiveness of contraceptive methods has been assessed against a number of outcomes which were agreed by the GDG on the basis of their relevance to patients and professionals. These outcomes are contraceptive effectiveness (measured by failure rates – pregnancy per 100 women years); impact on menstrual bleeding; discontinuation and acceptability of method; and impact on longer term reproductive health. Side effects from methods include hormonal effects – menstrual disturbances, skin effects, bone mineral density, mood (premenstrual symptoms and depression), and risks of thromboembolic disease. Specific consideration was given to the effectiveness and use of these methods in specific groups of women such as women who breastfeeding, teenagers, women at risk of sexually transmitted infection and HIV; women aged over 35 and women with other conditions such as diabetes, epilepsy and HIV which may impact on their contraceptive choices.

This is the second draft of the guideline that is available for stakeholder consultation.

2 Summary

2.1 Key recommendations

Contraceptive provision

2.1.1 Women requiring contraception should be provided with information and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. [D/GPP]

Counselling and provision of information

2.1.2 Women considering LARC methods should receive both verbal and written information that will enable them to choose and use the method effectively. This information should take into consideration their individual needs and should include:

- contraceptive efficacy
- risks and possible side effects
- advantages and disadvantages
- non-contraceptive benefits
- the procedure for initiation and removal/discontinuation
- duration of use
- when to seek help while using the method. [D/GPP]

Training of health professionals in contraceptive care

2.1.3 All health professionals advising women about contraceptive choices should be competent to:

- assist women to consider and compare the risks and benefits of all methods relevant to their individual needs
- manage common side effects [D/GPP]

2.1.4 All health professionals providing contraceptive care should ensure that they have an agreed mechanism in place for referring women for LARC if they do not provide LARC within their own practice/service. [D/GPP]

2.1.5 All health professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. [D/GPP]

2.2 Summary of recommendations

Chapter 3 Contraception and principles of care

3.1 Normal fertility

Health professionals should ensure that women and men understand that unprotected sexual intercourse risks pregnancy especially when it occurs in the days around ovulation. [C]

3.2 Contraceptive provision

Family planning is a human right. Women and men should have access to all types of licensed contraception available on the NHS and be free to choose the method that suits them best. [D/GPP]

Women requiring contraception should be provided with information and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. [D/GPP]

3.5 Counselling and provision of information

Women and men should be given accurate and detailed information, tailored to their needs, about all methods of contraception, including LARC. [D/GPP]

Women considering LARC methods should receive both verbal and written information that will enable them to choose and use the method effectively. This information should take into consideration their individual needs and should include:

- contraceptive efficacy

- risks and possible side effects
- advantages and disadvantages
- non-contraceptive benefits
- the procedure for initiation and removal/discontinuation
- duration of use
- when to seek help while using the method. [D/GPP]

Counselling about contraception should be sensitive to cultural differences and religious beliefs. [D/GPP]

Health professionals should be able to provide information that is in a format appropriate for women with special needs [D/GPP]

For women whose first language is not English, written information about contraceptive methods should be available in their preferred language. [D/GPP]

Health professionals should have access to interpreters for women who are not English speaking and/or advocates for women with sensory impairments or learning difficulties [D/GPP]

3.6 Contraceptive prescribing

A detailed medical history, including relevant family history, menstrual, contraceptive and sexual history, should be taken as part of the routine assessment of medical eligibilty for individual contraceptive methods. [D/GPP]

All health professionals helping women to make contraceptive choices should be familiar with nationally agreed guidance* on medical eligibility and recommendations for contraceptive use. [D/GPP]
(* This refers to the WHOMEC[16])

3.8 Acceptability

Women should be provided with the method of contraception

which is most acceptable to them provided it is not contraindicated for reasons of safety. [D/GPP]

3. 11 Contraception and sexually transmitted infection

All health professionals providing contraceptive advice should promote safer sex. [D/GPP]

All health professionals providing contraceptive advice should promote screening for STIs when appropriate [D/GPP]

All health professionals should be able to provide information about local services for STI screening, investigation and treatment [D/GPP]

Women using LARC should be encouraged to also use condoms with a new partner. [D/GPP]

3.12 User autonomy and consent

Women (couples) should have freedom of choice in contraceptive methods. [D/GPP]

3.13 The law relating to contraception for special groups

People with learning and/or physical disabilities should be supported in making their own decisions about contraception through referral to GPs or specialist clinics [D/GPP].

Contraception should be seen in terms of the needs of the individual rather than in terms of relieving the anxieties of carers and relatives. [D/GPP]

Where a person with a learning disability is unable to understand and take responsibility for decisions about contraception, carers and other involved parties should meet to address issues around contraceptive need and to establish a care plan for future support of the individual. [D/GPP]

Health professionals should be aware of the law relating to the provision of contraception for young people and for people with learning disabilities [D/GPP]

3.14 Training of health professionals in contraceptive care

All health professionals advising women about contraceptive choices should be competent to:

- assist women to consider and compare the risks and benefits of all methods relevant to their individual needs
- manage common side effects [D/GPP]

All health professionals providing contraceptive care should ensure that they have an agreed mechanism in place for referring women for LARC if they do not provide LARC within their own practice/service. [D/GPP]

All health professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. [D/GPP]

3.15 Cost-effectiveness of LARC methods versus other reversible contraceptive methods

LARC methods should be available in the NHS, since they are cost effective compared to other reversible contraceptive methods commonly used.

Chapter 4 Copper intrauterine devices (IUDs)

4.1 Introduction

Women should be advised that there is evidence that all copper IUDs probably act by both impairing gamete viability and inhibiting implantation. [C]

Women who are aged 40 and older at the time of copper IUD insertion can retain the device until they no longer require contraception. It is important that

this is discussed with women at fitting as it is outside the product license. [D/GPP]

4.2 Effectiveness

Health professionals should be aware that the TCu380A is the copper IUD of choice because of its effectiveness and licenced duration of action of 8 years. [B]

Women should be informed that the pregnancy rate associated with the use of IUDs with 375 mm^2 copper or above is less than 2 in 100 women over a 5-year period. [C]

3.3 Expulsion

Women should be advised that an IUD may be expelled but that this occurs in fewer than 1 in 20 women over a 3-year period. [C]

Women should be instructed how to check for the presence of the IUD threads and advised to do so regularly with the aim of recognising expulsion. [D/GPP]

3.4 Discontinuation and reasons for discontinuation

Health professionals and women should be made aware that up to 50% of women will stop using the IUD within 5 years. The most common reason for discontinuation is unacceptable vaginal bleeding. [C]

3.5 Adverse effects

Health professionals and women should be made aware of the risk of heavier bleeding and/or dysmenorrhea with IUD use. [C]

Heavier bleeding with IUD use can be treated with non-steroidal anti-inflammatory drugs and tranexamic acid. [B]

Women who find heavy bleeding in association with a copper IUD unacceptable may consider changing to a LNG-IUS (Levonorgestrel intrauterine system). [D/GPP]

Women with established iron-deficiency anaemia should not usually use a copper IUD. [D/GPP]

4.6 Common concerns and symptoms

Women should be informed that there is no evidence that the use of the IUD affects weight. [C]

Women should be advised that changes in mood and libido were similar whether using IUDs or LNG-IUS, and the changes are small. [C]

4.7 Risks

Women should be reassured that the overall risk of ectopic pregnancy with copper IUD use is reduced compared with using no contraception. However, women who become pregnant with an IUD in place should have intrauterine and ectopic pregnancy excluded. [D/GPP]

Women should be advised that in the event of IUD failure the risk of ectopic pregnancy is less than 0.2%. [C]

The presence of actinomyces-like organisms on a cervical smear in a woman with a current copper IUD requires an assessment to exclude pelvic infection.

Routine removal is not indicated in women without signs of pelvic infection. [D/GPP]

Women should be informed that the chance of developing pelvic inflammatory disease following a copper IUD insertion is very low in women at low risk of sexually transmitted infection, at less than 1% over 1 year. [C]

All women should be offered screening for STIs before IUD insertion and women at risk of STIs should be strongly encouraged to accept the offer. [D/GPP]

Where screening is not possible, or where screening has not been completed, use of prophylactic antibiotics is recommended in women with increased risk of STIs. [D/GPP]

Women should be reassured that the risk of uterine perforation at the time of IUD insertion is very low (less than 1 in 100). [C]

Women should be advised on symptoms of uterine perforation, which would warrant an early review. [D/GPP]

Women should be informed that the risk of perforation is related to the skill of the healthcare professional inserting the device. [D/GPP]

Women who become pregnant with the IUD in situ should be advised to consult early to exclude ectopic pregnancy. [D/GPP]

If the pregnancy is before 12 weeks and the IUD can be easily removed, it should be removed regardless of the woman’s intentions to continue or terminate the pregnancy. [D/GPP]

4.8 Return to fertility

Women should be informed that there is no evidence for any delay in return of fertility following removal or expulsion of the copper IUD.[C]

4.9 Details of method use

Health professionals fitting a copper IUD should have reasonably excluded relevant genital tract infection (cervical or pelvic) (chlamydia, gonorrhoea and pelvic inflammatory disease) by assessing sexual history, clinical examination and undertaking laboratory tests. [D/GPP]

Women with identified risks associated with uterine or systemic infection should have investigation, appropriate prophylaxis or treatment instigated prior to insertion of a copper IUD. [D/GPP]

Women should be advised of failure rates, benefits, risks and side effects of the copper IUD. [D/GPP]

Women should be informed that insertion of an IUD may cause pain and discomfort for a few hours and light bleeding for a few days following insertion and should be advised about appropriate pain relief. [D/GPP]

Women should be informed that the effect of the position of an IUD within the uterine cavity, in relation to contraceptive efficacy, is not known. [D/GPP]

Copper IUDs can be inserted at any time during a menstrual cycle. [D/GPP]

Copper IUDs can be inserted immediately or at any time following first and second trimester termination of pregnancy. [D/GPP]

Copper IUDs can be inserted from 4 weeks post partum irrespective of the mode of delivery if it is reasonably certain that the woman is not pregnant. [D/GPP]

4.10 Training of health professionals

IUDs should only be fitted by trained personnel with continuing experience of fitting at least one copper IUD or one LNG-IUS a month. [D/GPP]

4.11 Specific groups

IUDs may be inserted in adolescents. However, STI risk and Fraser competence should be considered. [D/GPP]

Women should be informed that nulliparity at any age is not a contraindication to IUD insertion. [D/GPP]

Women should be informed that women of all ages can use copper IUDs. [D/GPP]

Women should be informed that copper IUDs can safely be used by women who are breastfeeding. [C]

4.12 Medical conditions and contraindications

Women should be informed that diabetes poses no restriction to use of copper IUDs. [D/GPP]

Emergency drugs including anti-epileptic medication should be available at the time of fitting a copper IUD in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation. [D/GPP]

The IUD is a safe and effective method of contraception for women who are HIV positive or have AIDS. Safer sex using condoms should also be encouraged. [D/GPP]

4.14 Follow-up

A follow-up visit should be carried out after the first menses, or 3 to 6 weeks after insertion to exclude infection, perforation or expulsion. Thereafter, a woman should be advised to return at any time to discuss problems, if she wants to change her method, or when it is time to have the IUD removed. [D/GPP]

Chapter 5 Progestogen only intrauterine system (POIUS)

5.1 Introduction

Women should be advised that LNG-IUS as a contraceptive may act predominantly to prevent implantation and may not always prevent fertilisation. [D/GPP]

LNG-IUS is licenced 5 years. [C]

Women who are aged 45 and older at the time of LNG-IUS insertion and who are amenorrhoeic can retain the device until they no longer require contraception. It is important that this is discussed with women at the time of fitting as it is outside the product license. [D/GPP]

5.2 Effectiveness

Women should be informed that the pregnancy rate associated with the use of LNG-IUS is less than 1 in 100 women over a 5-year period. [C]

5.3 Expulsion

Women should be advised that a LNG-IUS may be expelled but this occurs in fewer than 1 in 10 women over a 5-year period. [C]

Women should be instructed how to check for the presence of the LNG-IUS threads, and advised to do this regularly with the aim of recognising expulsion. [GPP)

5.4 Discontinuation and reasons for discontinuation

Health professionals and women should be made aware that up to 60% of women will stop using the IUS within 5 years. The most common reasons for discontinuation are unacceptable vaginal bleeding and pain. [C]

The less common reasons for discontinuation are:

- hormone-related (non-bleeding)
- pelvic inflammatory disease [C]

5.5 Adverse effects

Women may be advised that oligoamenorrhoea or amenorrhoea is highly likely to occur by the end of the first year after LNG-IUS insertion. However, persistent bleeding and spotting are common for the first six months. [D/GPP]

5.6 Common concerns and symptoms

Women should be informed that there is no evidence that the LNG-IUS causes weight gain. However, some women discontinue the method citing weight gain as the reason, which may have occurred during the time of use as an unrelated event. [C]

Users of the LNG-IUS should be reassured that there is no increase above background prevalence in loss of libido or depression. [C]

Women should be informed that they may be at a theoretically increased risk for developing acne due to absorption of the progestogen, but that women do not discontinue the LNG-IUS for this reason frequently [C]

Women should be informed that all progestogen-only methods, including the LNG-IUS, may be used by women who have migraine with

or without aura. However, if the aura becomes more severe or frequent, the headaches should be investigated and alternative methods of contraception considered. [D/GPP]

5.7 Risks

Women with a history of venous thromboembolism (VTE) may use LNG-IUS. [D/GPP]

Women with a current VTE are advised not to use LNG-IUS (GPP)

Women with a history of previous ectopic pregnancy are at increased risk of future ectopic pregnancies. Women who become pregnant with a LNG-IUS in place should have intrauterine and ectopic pregnancy excluded. [D/GPP]

Women should be advised that in the event of a LNG-IUS failure the risk of ectopic pregnancy is less than 0.1%. [C]

The presence of actinomyces-like organisms on a cervical smear in a woman with a current LNG-IUS requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. [D/GPP]

Women should be informed that the chance of developing PID following LNG-IUS insertion is very low in women at low risk of sexually transmitted infections, at less than 1% over 1 year. [C]

All women should be offered screening for STIs before LNG-IUS insertion and women at risk of STIs should be strongly encouraged to accept the offer. [D/GPP]

Where screening is not possible, or where screening has not been completed, use of prophylactic antibiotics is recommended in women with increased risk of STIs. [D/GPP]

Women should be reassured that the risk of uterine perforation at the time of LNG-IUS insertion is very low at approximately 1 in 1000 over 5 years. [C]

Women should be advised on symptoms of uterine perforation, which would warrant an early review. [D/GPP]

Women should be informed that the risk of perforation is related to the skill of the health professional inserting the device.[D/GPP]

Women who become pregnant with the LNG-IUS in situ should be advised to consult early to exclude ectopic pregnancy. [D/GPP]

If the pregnancy is before 12 weeks and the LNG-IUS can be easily removed, it should be removed regardless of the woman's intentions to continue or terminate the pregnancy. [D/GPP]

5.8 Return to fertility

Women should be informed that there is no evidence for any delay in return of fertility following removal or expulsion of the LNG-IUS.[C]

5.9 Details of method use

Healthcare professionals fitting a LNG-IUS should have reasonably excluded relevant genital tract (cervical or pelvic) infection (chlamydia, gonorrhoea and PID) by assessing sexual history, clinical examination and if indicated, by appropriate laboratory tests. [D/GPP]

Women with identified risks associated with uterine or systemic

infection should have an investigation, appropriate prophylaxis or treatment instigated prior to insertion of the LNG-IUS. [D/GPP]

Women should be advised of failure rates, benefits, risks and side effects of the LNG-IUS. [D/GPP]

Women should be informed that the insertion of a LNG-IUS may cause pain and discomfort for a few hours and light bleeding for a few days following insertion and should be advised about appropriate pain relief. [D/GPP]

Women should be informed that the effect of the position of a LNG-IUS within the uterine cavity, in relation to contraceptive efficacy, is not known. [D/GPP]

A LNG-IUS can be inserted at any time during a menstrual cycle if it is reasonably certain the woman is not pregnant. [D/GPP]

A LNG-IUS can be inserted immediately or at any time following first and second trimester termination of pregnancy. [D/GPP]

A LNG-IUS can be inserted from 4 weeks post partum irrespective of the mode of delivery if it is reasonably certain the woman is not pregnant. Use before 6 weeks is outside the product license.[D/GPP]

5.10 Training of health professionals

IUDs should only be fitted by trained personnel with continuing experience of fitting at least one copper IUD or one LNG-IUS a month. [D/GPP]

5.11 Specific groups

LNG-IUS may be inserted in adolescents. However, STI risk and Fraser competence should be considered. [D/GPP]

Women should be informed that nulliparity at any age is not a contraindication to LNG-IUS insertion. [D/GPP]

Women should be informed that those of all ages can use LNG-IUS. [D/GPP]

Women should be informed that LNG-IUS can be safely used by breast feeding mothers. [D/GPP]

5.12 Medical conditions and contraindications

Women should be informed that diabetes poses no restriction to use of LNG-IUS. [D/GPP]

Emergency drugs including anti-epileptic medication should be available at the time of fitting a LNG-IUS in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation. [D/GPP]

The LNG-IUS is a safe and effective method of contraception for women who are HIV positive or have AIDS. Safer sex using condoms should also be encouraged. [D/GPP]

5.13 Drug interactions

Women and health professionals should be made aware that there is no evidence of reduced effectiveness of LNG-IUS when taking any other medication. [D/GPP]

5.14 Follow-up

A follow-up visit should be carried out after the first menses, or 3 to 6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be advised to return at any time to

discuss problems, if she wants to change her method, or when it is time to have the LNG-IUS removed. [D/GPP]

Chapter 6 Progestogen only injectable contraceptives (POICs)

6.1 Introduction

Women should be advised that progestogen-only contraceptive injectables work primarily by preventing ovulation. [C]

Depot medroxyprogesterone acetate (DMPA) should be repeated every 12 weeks and norethisterone enanthate (NET-EN) every 8 weeks. [C]

6.2 Effectiveness

Women should be advised that injectable contraceptives, when given at the appropriate intervals, have very low pregnancy rates, no higher than 0.4 in 100 at 2 years. Pregnancy rates with DMPA are lower than those with NET-EN . [C]

6.3 Discontinuation and reasons for discontinuation

Health professionals should know that as many as 50% of women using DMPA may discontinue by 1 year. [C]

Women should be informed that an altered bleeding pattern is a common reason for the discontinuation of use of DMPA. [C]

6.4 Adverse effects

Women should be informed that amenorrhoea is a common side effect of injectable contraceptives:

- it is more likely with DMPA than NET-EN
- it is more likely as time goes by

- it is not harmful. [C]

Health professionals should be advised that non-hormonal treatment with mefenamic acid or hormonal treatment with ethinylestradiol may be helpful in managing bleeding problems associated with DMPA use. [D/GPP]

6.5 Common concerns and symptoms

Women should be advised that DMPA use may be associated with an increase of 2 to 3 kg in weight over 1 year. [C]

Women should be advised that the use of DMPA is not associated with depression. [C]

Women should be advised that the use of DMPA is not associated with acne. [C]

Women should be informed that all progestogen-only methods, may be used by women who have migraine with or without aura. Women should be advised that the use of DMPA is not associated with headaches. [C]

6.6 Risks

Health professionals should know that DMPA, and probably NET-EN, are medically safe for women to use if there is a contraindication to oestrogen. [D/GPP]

All women should be advised that the use of DMPA is associated with a small loss of bone mineral density, which may be recovered when the method is discontinued. [B]

There is no evidence that the use of DMPA increases the risk of fracture. [B]

All women who wish to continue DMPA beyond 2 years should have their individual clinical situation reviewed and be supported in their choice. Their continued use of the method should be reviewed at regular intervals.[D/GPP]

Care should be taken in recommending DMPA to adolescents but DMPA may be given if other options are not suitable or acceptable. Their individual clinical situation should be reviewed at regular intervals.[D/GPP]

If pregnancy occurs during the use of DMPA there is no evidence of harm to the fetus. [D/GPP]

6.7 Return to fertility

Women should be informed that there could be a delay of up to 1 year in the return of fertility after discontinuation of injectable contraceptives. [C]

Women stopping injectable contraceptives but not wishing to conceive should be advised to use a different method of contraception immediately. [D/GPP]

6.8 Details of method use

The gluteal, lateral thigh and deltoid are all acceptable sites for injectable contraceptives. [D/GPP]

Women should be advised of failure rates, benefits, risks and side effects of injectable contraceptives. [D/GPP]

Injectable contraceptives may be started up to and including the fifth day of the menstrual cycle. No additional contraceptive protection is needed. Injectables contraceptives may be given at any other time in the cycle if it is reasonably certain that the woman is not pregnant; additional contraception should be used for the first 7 days after injection. [D/GPP]

Repeat injections of DMPA should be given every 12 weeks and for NET-EN every 8 weeks. [C]

Women attending up to 2 weeks late may be given DMPA or NET-EN injection without the need for additional contraceptives if it is reasonably sure that they are not pregnant. [D/GPP]

DMPA and NET-EN may be given immediately following abortion in any trimester (spontaneous or induced). [D/GPP]

DMPA and NET-EN may be initiated at any time post partum if it is reasonably certain the woman is not pregnant.[D/GPP]

6.10 Specific groups

Care should be taken in recommending DMPA to women aged over 40 because of the possible effect on bone mineral density but in general the benefits outweigh the risks. [D/GPP]

Women with a body mass index over 30 can safely use DMPA and NET-EN. [D/GPP]

Breastfeeding women may be advised that they can use injectable contraceptives immediately after childbirth if other methods are unacceptable. [D/GPP]

6.11 Medical conditions and contraindications

Women should be informed that progestogen-only injectable contraceptives are not contraindicated for women with diabetes. [D/GPP]

The use of DMPA may be associated with a reduction in the frequency of seizures in women with epilepsy requiring contraception.[D/GPP]

There is no evidence to suggest a causal relationship between the use of DMPA and an increased risk of STI or HIV acquisition. Women at increased risk of STI, including HIV/AIDS, may use DMPA and NET-EN. POICs do not protect against STI/HIV and if there is a risk, the correct and consistent use of condoms in addition to the injectable contraceptives is recommended. [D/GPP]

6.12 Drug interactions

It is not considered necessary to avoid the use of injectable contraceptives in women taking liver enzyme-inducing medication or to reduce the injection interval. [D/GPP]

6.13 Follow-up

A repeat follow-up visit is required every 12 weeks for DMPA users and 8 weeks for NET-EN users. [D/GPP]

7. Progestogen only subdermal implants (POSDIs)

7.1 Introduction

Women should be advised that implants work by altering the endometrium and cervical mucus and in a proportion by preventing ovulation. [C]

Women should be informed that Implanon lasts for 3 years. [C]

7.2 Effectiveness

Women should be advised that subdermal implants, including Implanon, have very low pregnancy rates (less than 0.1 in 100 over 3 years). [C]

7.3 Discontinuation and reasons for discontinuation

Women should be aware that up to 33% of women will discontinue Implanon within 3 years because of irregular bleeding. Fewer than one in ten women will discontinue for other reasons including hormonal effects. [C]

7.4 Adverse effects

Women should be advised that it is highly likely that their bleeding pattern will change while using Implanon. [C]

One in five women will have no bleeding while almost half will have frequent, infrequent or prolonged bleeding with Implanon use. Women should be advised that bleeding patterns are unlikely to become more regular over time. [C]

Women should be advised that dysmenorrhoea may improve during Implanon use. [C]

Health professionals should be advised that non-hormonal treatment with mefenamic acid or hormonal treatment with ethinylestradiol or mifepristone is moderately effective in stopping irregular bleeding during implant use. [B]

7.5 Common concerns and symptoms

Women should be informed that the use of Implanon is not associated with weight changes in the short-term. [C]

Women should be informed that mood changes may occur with the use of Implanon. [C]

Women should be reassured that Implanon use is not associated with a change in libido. [C]

Women should be informed that acne may occur during Implanon use.[C]

Women should be informed that all progestogen-only methods may be used by women who have migraine with or without aura. Women should be reassured that there is no evidence that headaches will be increased by the use of Implanon. [C]

7.6 Risks

Subdermal implants are medically safe for women to use if there is a contraindication to oestrogen. [C]

Women should be informed that there is no evidence for a clinically significant effect of Implanon on bone mineral density. [C]

Women should be informed that the risk of ectopic pregnancy while using Implanon is theoretically extremely low, and less than that of women not using contraception. [C]

Providers and women should be advised that there is no evidence for a teratogenic effect of Implanon. Nevertheless, should pregnancy occur and be continued, the implant should be removed. [D/GPP]

7.7 Return to fertility

There is no evidence for any delay in return of fertility following removal of contraceptive implants. [C]

7.8 Details of method use

Women should be advised of failure rates, benefits, risks and side effects of contraceptive implants.[D/GPP]

Implants may be inserted at any time if it is reasonably certain that the

woman is not pregnant. If the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be advised for 7 days following insertion. [D/GPP]

Implants may be inserted immediately following abortion in any trimester (spontaneous or induced). [D/GPP]

Implants may be initiated at any time post partum if it is reasonably certain the woman is not pregnant. [D/GPP]

Women may be informed that Implanon insertion and removal both cause some discomfort and bruising but that technical problems are unusual (less than 1 in 100). [C]

Women should be informed that if an Implanon has migrated or is too deep to be removed, an ultrasound localisation and removal by an expert will be required.[D/GPP]

7.9 Training of health professionals

Subdermal implants should be inserted and removed only by health professionals trained in the procedures. [D/GPP]

7.10 Specific groups

Women and adolescents should be informed that there is no evidence that effectiveness or adverse effects of implants vary with the age of the user. However, STI risk and Fraser competence (for adolescents) should be considered.[C]

Providers and adolescents should be aware that pregnancy rates are lower among adolescents using implants compared with those using oral contraception or condoms. [C]

Women should be advised that, as potential users of Implanon, there is no evidence for a higher rate of pregnancy among women weighing over 70kg. [D/GPP]

Subdermal implants can safely be used by women who are breastfeeding and may be inserted at any time post partum if there has been no risk of pregnancy. [D/GPP]

7.11 Medical conditions and contraindications

Women should be informed that Implanon is not contraindicated for women with diabetes. [C]

There is no evidence to suggest a causal relationship between the use of implants and an increased risk of STI or HIV acquisition. Women at increased risk of STI including HIV/AIDS may use implants. Subdermal implants do not protect against STI/HIV and if there is a risk, the correct and consistent use of condoms in addition to the implants is recommended. [D/GPP]

7.12 Drug Interactions

Implanon is not recommended as the sole method of contraception for women concurrently taking enzyme-inducing drugs. [D/GPP]

7.13 Follow-up

No routine follow-up after implant insertion is required. [D/GPP]

2.3 LARC selection algorithm

3 Contraceptive use and principles of care

3.1 Normal fertility

During sexual intercourse, spermatozoa are deposited into the vagina. They migrate through the cervix and uterine cavity to the fallopian tubes where, if they meet the egg, fertilisation can take place. The embryo then travels down the fallopian tube and enters the uterine cavity where implantation takes place. The length of a menstrual cycle varies between 21 days and 35 days. Ovulation usually takes place 12–16 days before the start of the next period. For a woman with a 28-day menstrual cycle (the first day of menstruation being day 1), ovulation takes place around day 14. After ovulation, the egg usually lives for up to 24 hours. After ejaculation, sperm can survive for up to 7 days in the genital tract.[17][EL=3] Most pregnancies can be attributed to sexual intercourse during a 6-day period ending on the day of ovulation,[18;19][EL=3] with the highest estimated conception rates associated with intercourse 2 days before ovulation.[20][EL=3] This information is used as the basis for methods of contraception relying on periodic abstinence (natural family planning) and informs the advice relating to the use of emergency contraception and what action to take when oral contraceptive pills are missed. Misunderstandings about inherent fertility and about the time in the cycle when pregnancy is most likely to occur lead to incorrect and inconsistent use of barrier methods and oral contraceptives.

In the general population it is estimated that 84% of women would conceive within 1 year of regular unprotected sexual intercourse. This rises cumulatively to 92% after 2 years and 93% after 3 years.[21;22]

The conception rate per menstrual cycle is known as fecundability. Natural female fertility declines with age.[23][EL=3] The decline with age in rates of conception is seen after 30 years of age and is more marked after age 35 years.[24;25][EL=3]

Recommendation:

Health professionals should ensure that women and men understand that unprotected sexual intercourse risks pregnancy especially when it occurs in the days around ovulation. [C]

3.2 Contraceptive provision

In 1994 at the International Conference on Population and Development (ICPD) in Cairo, Egypt, government delegations from 179 countries, including the UK, agreed a Programme of Action to stabilise the world's population. The Programme of Action defined reproductive rights and stated that people should have the freedom to decide if, when, and how often to have children. ICPD further called for universal access to a full range of high-quality, affordable, accessible and convenient sexual and reproductive health services.[26]

Since 1972 contraception has been provided free of prescription charges in the UK. It is provided by general practitioners, community (NHS) family planning clinics (FPCs) and, increasingly, in some not-for-profit charitable clinics such as Brook (usually limited to young people under 25). In Great Britain in 2003/04 almost 57% of women aged 16-49 had used at least one service in the past five years.[1] Most (81%) had visited their GP surgery but 32% had used a community FPC. Not all settings provide all methods of contraception, and not all doctors are competent to fit intrauterine devices (or systems) or contraceptive implants. (Refer to Medical Foundation for AIDS and Sexual Health (MedFASH) Sexual Health Standards http://www.medfash.org.uk/). Women attending FPCs are more likely to use a long acting method of contraception, particularly implants and IUD/IUS, than those consulting their GP.

In the UK, because contraceptives are provided free of charge, cost plays no part in determining an individual's choice of method and does not influence continuation rates or method switching. In countries where contraceptives are

not free and where the consultation and procedure may also be charged to the user, cost plays a much bigger part in uptake and continuation and data from these countries must be extrapolated to the UK with caution. In one state in the USA in the early 1990s women were offered a payment of $500 if they had Norplant inserted and further annual payments of $50 for each year they kept it.[27] Cost however is relevant to the service provider and may determine the choice of methods available in some settings. Some local formulary committees withhold approval of the newer, more expensive contraceptive methods (such as the contraceptive patch and newer brands of oral contraceptive pill) arguing that there is no evidence of superiority over existing cheaper methods. Providers' attitudes towards, knowledge of, and preferences for particular methods of contraception influence the choices made by the users.[28] If women/couples are not informed about all available methods of contraception, their choices are restricted.

Recommendations:

Family planning is a human right. Women and men should have access to all types of licensed contraception available on the NHS and be free to choose the method that suits them best. [D/GPP]

Women requiring contraception should be provided with information and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. [D/GPP]

3.3 Contraceptive prevalence

Almost everyone in the UK uses contraception at some time in their lives. Contraceptive prevalence has increased dramatically in the last thirty years. In Great Britain in 2003/04, 52% of all women aged 16-49 were using a reversible method of contraception and just under a quarter had either been sterilised (11%) or had a partner who was sterilised (12%).[1] Of women 'at risk' of pregnancy (i.e. in a heterosexual relationship, presumed fertile and not actively trying to fall pregnant) only 2% were not using any method of contraception.[1]

The pattern of contraceptive use varies with age, ethnicity and race, marital status and fertility intentions and education.[29] In Great Britain in 2004 the oral contraceptive pill was the most popular method of contraception among women aged 16 to 49 (25% of women use it) while the next most popular method was the male condom (23% of women)[1] (Table 3.1). Long acting methods of contraception (injectables, implants, intrauterine devices and systems) are used by 8% of women. In general the IUD/IUS tends to be adopted by older, parous women while Depo Provera and Implanon are more commonly used by younger women and women without children. Most hormonal methods of contraception have an effect on vaginal bleeding patterns.[30] For women with certain religious beliefs, methods which cause irregular bleeding can be a major inconvenience. Not all methods are available in all countries and not all available methods are marketed in the UK. Women coming to the UK from elsewhere may be using a method which is unavailable or (e.g. norethisterone oenanthate NET-EN) only licensed for short term use in the UK.

The average age of first intercourse in the UK has stabilised for both men and women at 16 years[31] and the average age of first childbirth has risen to almost 30. Since the mean age of menopause is 51 and the total fertility rate in the UK in 2004 is 1.7. Most women/couples will need to use contraception for more than 30 years.[32]

Unintended pregnancy

Despite the widespread use of contraception, unintended pregnancy is common. In England and Wales the abortion rates for the quarter January-March 2004 was 18.6 per 1000 women of reproductive age. The abortion rate was highest at 33.6 per 1000 for women in the 20-24 age group. The abortion rates were 28.1 per 1000 women for women in the 16-19 age group and 3.9 per 1000 women in women under 16 years of age.[33][EL=3] Not all unintended pregnancies end in abortion. It has been suggested that as many as 30% of pregnancies which end in childbirth are unplanned when they are conceived.[34]

A UK questionnaire survey of pregnant women (n=12106) designed to investigate the association of duration of OC usage with time to conception reported that 29.4% of the pregnancies were unintentional. [35][EL=3] Most data suggest that true method failure accounts for fewer than 10% of unintended pregnancies, the rest arising either because no method was used at the time conception occurred (30-50%) or because the method was used inconsistently or incorrectly.[36-38] Failure due to inconsistent use of oral contraception and condoms was reported to be the main cause of pregnancy among women undergoing termination. [39;40][EL=3]

It is important for repeat unwanted pregnancies to be prevented rather than aborted. Repeat abortions are common, estimated to be between 27% to 48% of all induced abortions.[41-45][EL=3]

Teenage pregnancy

In 2001, 7.4 per cent of all births in England and Wales were to women aged under 20. [46][EL=3] In 2003, the under 18 conception rate was 42.3 per 1000 women (aged 15 -17) and 46% of these conceptions resulted in legal abortions. In 2002, the under 16 conception rate was 7.9 per 1000 women (aged 13 – 15) and 55.7% of these conceptions led to abortions. [47][EL=3] In 2003, the age-standardised abortion was 17.5 per 1000 resident women aged 15-44 (17.0 in 2002). The abortion rate was the highest at 31.4 per 1000, for women in the 20-24 age group.(30.7 in 2002). The under-16 abortion rate was 3.9 in 2003 compared with 3.7 per 1000 in 2002. Infant mortality rates for children born to teenage mothers are 1.3-fold higher than that for total births, due mainly to low birth weight and congenital anomalies. [48][EL=3]

Based on a report by the Social Exclusion Unit (SEU) on Teenage Pregnancy in 1999, [49] the DOH has developed a national strategy to:

- reduce the rate of teenage conceptions, with the specific aim of halving the rate of conceptions among under 18s by 2010, with an interim reduction of 15% by 2004;

- set a firmly established downward trend in the under 16 conception by 2010;
- increase the participation of teenage parents in education and work, to reduce their risk of long term social exclusion.[50][EL=4]

3.4 Efficacy and effectiveness of contraception

The effectiveness of a method of contraception is judged by the failure rates associated with its use. Failure rates for currently available methods are shown in Table 3.2.[51](NB. This table does not include any data on Implanon). The rates are estimated from US studies and show the percentage of couples who experience an accidental pregnancy during the first year of use of each method.[52] The effectiveness of a contraceptive depends on its mode of action and how easy it is to use.[53] Pregnancy rates during perfect use of a method reflect its efficacy. If a method prevents ovulation in every cycle in every woman, it should have an efficacy of 100%, since if there is no egg there can be no conception. Only if a mistake is made, or if the method is used inconsistently, will a pregnancy occur. Imperfect use with these long acting methods of contraception is usually due to provider error - undetected uterine perforation during IUD insertion for example. The contraceptive implant Implanon® inhibits ovulation for three years and is extremely effective as the user has to take no action once the implant is inserted.[54] The combined pill is probably as effective at preventing ovulation and pregnancy; rates for perfect use are only 0.1 in 100. True pill failures are due to incomplete inhibition of ovulation mainly among women who metabolise the pill rapidly. Inhibition of ovulation however depends on the pill being taken perfectly. With imperfect use ovulation can occur and typical-use failure rates are 8 in 100 (Table 3.2).[51] LARC methods are more effective than barrier methods or oral contraceptives because they demand much less - or are independent of – the need for compliance. Failure rates associated with typical use are virtually the same as those associated with perfect use. Active steps must be taken if a woman wishes to stop using an IUD, IUS or implant while discontinuation of other methods (including injectables) is passive. In a cohort study of US teenagers using Norplant® (n=200), pills (100) or condoms (99), there were no

pregnancies among Norplant users while one third of teenagers using pills or condoms had conceived.[55]

Pregnancy rates are still often described by the Pearl Index (PI), the number of unintended pregnancies divided by the number of women years of exposure to the risk of pregnancy while using the method. The Pearl Index is expressed as the pregnancy rate per 100 women-years (a woman year is defined as 13 menstrual cycles).[56] If, out of 100 women using a contraceptive method for 13 cycles, one becomes pregnant the PI is 1.0. However failure rates of most methods decrease with time since women most prone to failure will become pregnant early after starting a method.[52] With time, a cohort of couples still using a method increasingly comprises of couples unlikely to fall pregnant (because they are good at using the method, highly motivated to avoid pregnancy, or are infertile). So the longer a contraceptive trial lasts, the lower the pregnancy rate is likely to be. Furthermore, failure rates in most clinical trials are often underestimated because all of the months of use of the method are taken into account when calculating failure rates, regardless of whether or not intercourse has occurred during that cycle. For long acting methods of contraception such as IUDs and implants, the pregnancy rate with time (cumulative pregnancy rate) is more informative and is presented as the standard measure of contraceptive effectiveness in this guideline.

The effectiveness of all methods of contraception is likely to be higher in clinical trials than in real life[57] since trial participants are not representative of the general population of contraceptive users and the routine daily recording of contraceptive use (mandatory in trials) enhances adherence. Randomised, placebo-controlled trials are widely regarded as the gold standard for determining effectiveness of drugs and other therapeutic interventions. Use of a placebo is unethical in trials of a contraceptive method since all contraceptive users wish to avoid pregnancy. While RCTs between like methods (one type of copper IUD versus another, or one brand of combined pill versus another) are possible, it is extremely difficult to recruit people willing to participate in RCTs comparing different types of contraceptive. In

developed countries most women are well informed about contraceptive choice and have strong views about methods they do – and particularly do not – want to use.[58;59]

The effectiveness of some hormonal methods of contraception is affected by the body weight of the user. Women of a high body weight have higher failure rates with pills,[60] Norplant[61;62] and patches.[63] Body weight may also influence bleeding patterns; women with a low body weight are more likely to experience amenorrhoea while using Norplant.[16] Trials of effectiveness in populations of women with a much lower body weight than that of the average UK female population (such as women from Thailand or Indonesia) may underestimate failure rates and underestimate the incidence bleeding irregularity.

3.5 Counselling and provision of information

Accurate, up-to date information is essential to enable users to make an informed and voluntary choice of a contraceptive method. User satisfaction and successful use of contraception depend on adequate knowledge and accurate perceptions of the method. Counselling is a face-to-face communication in which one person helps another make decisions and act on them.[64] The ultimate goal of contraceptive counselling is to allow women to choose a method they feel most comfortable with and will continue using, taking into account their lifestyle preferences and concerns. Contraceptive counselling helps women to learn more about contraception and combats misinformation about contraceptive methods. In addition, counselling can provide the basis for informed consent and set the stage for increased user satisfaction with the method chosen. Informed choice is facilitated by promoting understanding of the relative effectiveness of the method; how it works; insertion and removal procedures; correct use; common side effects; health risks and benefits; when to seek medical advice; information on return to fertility after discontinuation; and advice on STI protection and sexual health.

3.5.1 Knowledge and concerns about contraceptive methods

Using a series of semi-structured focus groups, a UK study assessed women's knowledge of the effectiveness of different contraceptive methods and of the risks of thrombosis associated with hormonal contraceptives. Women tended to underestimate the effectiveness of hormonal contraceptives, particularly implants, and to over-estimate the risk of thrombosis associated with hormonal contraceptives.[65][EL=3] Many were more concerned about the adverse effects (especially bleeding irregularities and weight gain), than about effectiveness.

A US questionnaire survey (n=249, aged 12-20 years) reported that knowledge of Norplant among the general adolescent population was poor. However, young women who were using Norplant were 11 times more likely than those using other types of contraceptive methods to be more knowledgeable about Norplant, having received additional counselling from health care providers.[66][EL=3]

3.5.2 Source of information

An audit in the UK undertaken to inform a questionnaire developed to identify local demand and interest in Levonogestrel intrauterine system (LNG-IUS), reported that women received information about a broad range of contraception available, but that 33% of women came with their 'own agenda' and were sure before the visit about which method they wanted.[58][EL=3]

One survey (n=4500) in the Netherlands reported that women were well-informed about all aspects of contraception as a result of formal and informal education at school, from their families, and by the media. Most of these women (86%) viewed their contraceptive choices as their own. The general practitioner was regarded as the most important and reliable source of information (73%).[59][EL=3]

3.5.3 Effect of information on satisfaction and continuation

A Finnish survey of LNG-IUS users (n=17360) evaluated the impact of advance information on user satisfaction with the method. User satisfaction was associated with information (on menstrual disturbances, pelvic inflammatory disease, greasiness of hair or skin, and the possibility of pregnancy) given at the time the LNG-IUS was inserted. Women who received information about the possibility of amenorrhoea were more satisfied when compared with the women who were less well informed (OR 5.0, 95% CI 4.1 to 5.9).[67][EL=3]

A survey of new DMPA users in Bolivia (n=352) reported that women who received information on the efficacy, side effects and amenorrhoea of DMPA had higher continuation rates those who did not receive such information. Women advised to return to the clinic if experiencing problems were 2.7 times more likely to continue DMPA at 1 year, and those advised of amenorrhoea were 2.5 times more likely to return for a second injection of DMPA compared to women who did not receive such information from the provider.[68][EL=3] Similar findings were reported from a study of 350 new DMPA users in Mexico where detailed, structured, pre-treatment counselling resulted in fewer method discontinuations at 12 months compared with routine contraceptive counselling (15% versus 39% overall and 9 % versus 32% for menstrual disturbance including amenorrhoea).[69][EL=1+]

One RCT (n=636) in the UK assessed the effectiveness of providing educational leaflets versus verbal information in improving knowledge of contraception in women taking the combined pill. Baseline knowledge of contraception in the control group was poor. Written information had a significant effect on knowledge of factors associated with pill failure. Improvement in knowledge occurred with the provision of summary leaflets (adjusted OR 4.04, 95% CI 1.68 to 9.75), the Family Planning Association's leaflet (OR 3.43, 95%CI 1.45 to 8.09) and asking questions (OR 3.03, 95% CI 1.30 to 7.00). This study suggested that provision of educational leaflets on contraception and/or asking women relevant questions, though time-

consuming, may help improve women's knowledge of contraception.[70][EL=1+]

3.5.4 Method of information giving

The provision of written information may enhance understanding. One RCT (n=461) in the US evaluated three different approaches to increase women's understanding of risk of pregnancy associated with different contraceptive methods. A table with categories of contraceptives communicated relative contraceptive effectiveness better than the tables with numbers. However, without the presentation of the numbers, women grossly overestimated the absolute risk of pregnancy while using contraception. A table presenting a combination of categories of contraceptives and a general range of risk for each category (WHOMEC) may provide the most accurate understanding of both relative and absolute pregnancy risk.[71][EL=1-]

A survey (n=211) in the US reported that women relied heavily on their own experiences in assessing the risks and benefits of oral contraceptives. Written information was cited more frequently than medical personnel as a major source of information on cardiovascular and cancer risks and the benefits of OCs. The internet played a minimal, if any, role in educating women about OCs.[72][EL=3]

Recommendations:

Women and men should be given accurate and detailed information, tailored to their needs, about all methods of contraception, including LARC. [D/GPP]

Women considering LARC methods should receive both verbal and written information that will enable them to choose and use the method effectively. This information should take into consideration their individual needs and should include:

- **contraceptive efficacy**

- **risks and possible side effects**
- **advantages and disadvantages**
- **non-contraceptive benefits**
- **the procedure for initiation and removal/discontinuation**
- **duration of use**
- **when to seek help while using the method. [D/GPP]**

3.5.5 Specific groups

One survey (n=406) in US which examined the relationship between reading ability and knowledge of family planning, reported that women with low reading skills were 2.2 times more likely to want to know more about birth control methods (95% CI 1.1 to 4.4). They were 4.4 times more likely to have incorrect knowledge about when they were most likely to become pregnant (95% CI 2.1 to 9.0) than women with good reading skills. This raised additional questions of whether women with low reading skills understand the concept of informed consent prior to accepting contraceptive use.[73][EL=3]

An interview survey (n=32) of Somalian women attending a UK Well Women Clinic reported that effective contraceptive care and service provision needed to take into account the cultural interpretation of reproduction and family planning within a wider social and religious context in order to meet the needs of these women.[74][EL=3]

Recommendations:

Counselling about contraception should be sensitive to cultural differences and religious beliefs. [D/GPP]

Health professionals should be able to provide information that is in a format appropriate for women with special needs. [D/GPP]

For women whose first language is not English, written information about contraceptive methods should be available in their preferred language. [D/GPP]

Health professionals should have access to interpreters for women who are not English speaking and/or advocates for women with sensory impairments or learning difficulties. [D/GPP]

3.6 Contraceptive prescribing

Most contraceptive users are young and medically fit and can use all available methods safely. However, a few medical conditions are associated with theoretical increased health risks with certain contraceptives, either because the method adversely affects the condition (for example, combined hormonal contraceptives may increase the risk of a woman with diabetes developing cardiovascular complications), or because the condition or its treatment affects the contraceptive (some anti-epileptic drugs interfere with the efficacy of hormonal methods). Since most trials of new contraceptive methods deliberately exclude subjects with serious medical conditions, there is little direct evidence on which to base sound prescribing advice. In an attempt to produce a set of international norms for providing contraception to women and men with a range of medical conditions which may contra-indicate one or more contraceptive methods, WHO has developed a system to address medical eligibility criteria for contraceptive use (WHO-MEC).[75] Using evidence-based systematic reviews,[76] the document classifies conditions into one of four categories. Category 1 includes conditions for which there is no restriction for the use of the method while category 4 includes conditions which represent an unacceptable health risk if the contraceptive method is used (absolutely contraindicated). Classification of a condition as category 2 indicates that the method may generally be used but that more careful follow-up is required. Category 3 conditions are those for which the risks of the methods generally outweighs the benefits (relatively contraindicated). Provision of a method to a woman with a category 3 condition requires careful

clinical judgement since use of that method is not recommended unless there is no acceptable alternative. The WHO-MEC document is available on the web[16] and a system is in place to incorporate new data into the guidelines as it becomes available. A UK version of the WHO-MEC document is currently under development by the FFPRHC.

In an attempt to provide evidence-based guidance on safe and effective contraception, the WHO produced the Selected Practice Recommendations for Contraceptive Use.[76;77] The document has been adapted by the FFPRHC for use in the UK and provides guidance on assessment before providing contraceptives, including when to start a method, history taking, follow-up, and the management of common side effects.[78]

The vast majority of women who use hormonal contraception do not have any medical problems and they are young. Providers need to recognise the very few who may be at risk of the rare but serious complications of hormonal contraception. Taking a careful history (including family history) and observing obvious physical characteristics (like obesity) provides a lot of useful information. The WHO distinguishes between examinations and investigations which are essential for safe prescribing of contraception from those which 'do not contribute substantially to safe and effective use of the contraceptive method' but which are commonly done.[76] Routine breast and pelvic examination, cervical smears and blood tests such as the measurement of serum cholesterol fall into this category. The only tests considered mandatory in the UK are the measurement of blood pressure before starting combined hormonal contraception and pelvic examination before IUD/IUS insertion.

The UKSPR, in agreement with the WHO, recommends the ideal time in the cycle when a particular method of contraception should be initiated and how best to switch methods. Recognising that this may not always be the most convenient time, the UKSPR further recommends that all methods can be started at any time in the cycle provided it is reasonably certain that the woman is not pregnant. It is not necessary to undertake pregnancy testing before a method is started, even later in the cycle. Pregnancy can be

excluded by taking a menstrual and contraceptive history and asking about sexual activity. A test is indicated only if the history suggests that there is a risk that the woman might be pregnant.

Recommendations:

A detailed medical history, including relevant family history, menstrual, contraceptive and sexual history, should be taken as part of the routine assessment of medical eligibilty for individual contraceptive methods. [D/GPP]

All health professionals helping women to make contraceptive choices should be familiar with nationally agreed guidance* on medical eligibility and recommendations for contraceptive use. [D/GPP]

(* This refers to the WHOMEC[16])

3.7 Health benefits of contraception

The non-contraceptive health benefits of LARC influence the uptake and continuation of the methods they are summarised below. It is not possible to quantify the potential savings to the NHS that these additional health benefits might make (for example, the LNG-IUS is also licensed for the management of menorrhagia; women who use the method for contraception may be much less likely to complain of menorrhagia than women who are sterilised). The non-contraceptive benefits have, therefore, not been included in the cost effectiveness models.

Most couples use contraception for over thirty years. Additional health benefits beyond pregnancy prevention offer significant advantages and influence acceptability. In a nationwide sample of 943 US women, satisfaction with oral contraception was most likely among women aware of the non-contraceptive benefits of the pill and who experienced few side effects.[68]

Existing combined hormonal methods improve menstrual bleeding patterns,

alleviate dysmenorrhoea, acne and sometimes pre-menstrual syndrome and reduce the risk of ovarian and endometrial cancer. Increasing numbers of women choose the LNG-IUS and DMPA because of the amenorrhoea they confer. One non-comparative study (n=165) in Austria assessed long-term acceptability of LNG-IUS and reported that cessation of menstruation occurred in 47% of women at 3 years, over 80% of whom considered this to be a positive change. [79][EL=3] A Peri-menopausal women appreciate the facility to continue using the LNG-IUS into the menopause when it can be used to deliver the progestogen component of HRT.

The non-contraceptive benefits can influence continuation rates of contraception. One study in the USA demonstrated that women who experienced troublesome dysmenorrhoea prior to using the COC were 8 times more likely to continue using the pill than women who did not complain of dysmenorrhoea.[80]

3.8 Acceptability

Continuation rates are often regarded as a surrogate for acceptability of a method. This is simplistic. Many factors determine acceptability and continuation of a method may only reflect that it is the best of a bad lot. In recent years clinical trials have routinely included questions on acceptability at regular follow-up intervals but this is at best a crude measure of what is a complex issue. There is evidence to demonstrate that the acceptability of a contraceptive method (and continuation rate) is increased when users are well informed about the side effects and risks.[68]

The current uptake of long-acting reversible contraception in Great Britain is low (less than 10 % of contraceptive usage in 2003/4).[1] In a national survey of 1688 US women (where fewer than 2% used contraceptive implants and under 3%, injectables) women gave three major reasons for not using long-acting contraceptives: lack of knowledge; fear of side effects/risks and satisfaction with the method they were currently using. Women aged 30 or older and those with a college education were half as likely as younger

women and those without college education to mention fear of side effects as their main reason for not using implants.[81][EL=3] Important reasons for choosing a contraceptive included: how well it works[65;70;71], ease of use and protection against STI and HIV.[71] Contraceptive choice is strongly influenced by the provider's views and by the advice and information that he/she gives to the potential user. Providers may hold very different views from users. In a study of the acceptability of methods of contraception which confer amenorrhoea[82], providers thought that having a regular period was important to their clients while women themselves did not feel that it was important. The methods which a provider is able to offer also influences contraceptive choice. If a provider is unable to insert contraceptive implants, he/she is less likely to offer the method or, indeed, to be sufficiently well informed to give good information. Women may settle for a method which is easily available from their GP rather than have to travel to another service to obtain something different.

Acceptability of the chosen method is likely to be fundamental to correct and consistent use and to continuation. If a woman is unhappy with her method, for whatever reason, she is likely to discontinue it. If choice determines effective use and continuation, it can be argued that it should supersede considerations of cost.

Recommendation:
Women should be provided with the method of contraception which is most acceptable to them provided it is not contraindicated for reasons of safety. [D/GPP]

3.9 Compliance/adherence/concordance

Many couples use contraception inconsistently and/or incorrectly. Inconsistent or incorrect use accounts for the difference between perfect and typical use failure rates. Some methods are easier to use than others. The IUD/IUS and implants are inserted and removed by a health professional and are completely independent of compliance for efficacy. Their failure rates are

accordingly very low (Table 3.2)[83] and typical and perfect use rates are almost the same. Progestogen-only injectables last 12 weeks, but still demand the motivation and organisational skills required to attend for repeat doses. Compliance with the oral contraception is not easy. In one US study, 47% of women reported missing one or more pills per cycle and 22% reported missing two or more pills per cycle.[28] In a study using electronic diaries to record compliance, 63% of women missed one or more pills in the first cycle of use, and 74% in the second cycle.[53] Typical use failure rates are even higher with methods of contraception (condoms, diaphragms, withdrawal and natural family planning) which rely on correct use with every act of intercourse.

A descriptive review assessed the impact of health concerns on adherence to hormonal contraceptives. It reported that contraceptive-related knowledge among sexually active adolescents was poor and the general public had many concerns about the safety of hormonal contraception. The development of side effects, especially those related to menstruation, caused adolescents and young women to feel that their general and reproductive health was being threatened. Counselling tailored to address specific reasons for non-adherence in this population may be beneficial.[84][EL=3]

3.10 Discontinuation

In an international review of discontinuation rates after one year of use of hormonal contraception, rates varied from 19% (for Norplant) to 62% (the combined pill).[85] Many of these data come from clinical trials in which continuation rates are almost always higher than in 'real life'. Data specific to the UK are lacking. Discontinuation rates are higher for methods which do not require removal by a health professional as is clear from Table 3.3[83](NB. This table does not include any data on Implanon), which shows the percentage of couples in the USA still using each method at the end of one year. Reasons for discontinuation are often associated with perceived risks and with real or perceived side effects. In a US study of 1657 women initiating or changing to use a new contraceptive pill, 32% of new starts and 16% of switchers had

discontinued the method within six months. Of those who discontinued, 46% did so because of side effects (most of which they did not discuss with a health professional and most of which would have resolved themselves within weeks).[28] In Sweden a common reason for discontinuation of the oral contraceptive pill is weight gain (perceived to be caused by the pill) and fear of health risks such as breast cancer.[30]

Discontinuation rates from countries where access to contraception is limited and/or expensive may differ to those in the UK, for example, in developing countries. Similarly, data from countries where women are characteristically of significant lower body weight (such as Indonesia or Thailand) than women in the UK, may overestimate the effectiveness of hormonal methods of contraception and the side effect profile.

Continuation rates influence the effectiveness of contraception, since women often change to a less effective method or spend some weeks or months using no method while they decide what to use next. More than four fifths of women in the US study who stopped the pill, despite being at risk of pregnancy, either failed to adopt another method or changed to a less effective one.[86]

Data from the US National Survey of Family Growth demonstrate high rates of method switching (61% of unmarried women will change their method over the space of two years).[87] Switching to a less effective method is common.[88] Data specific to the UK are lacking.

Continuation rates of long acting methods of contraception are also fundamental to cost effectiveness. A method which costs £100 works out at £1.66/month if used for five years; discontinued after only one year of use the cost is £8.33/month.

3.11 Contraception and sexually transmitted infection

Sexual activity not only risks pregnancy but also sexually transmitted infection

including HIV. Methods of contraception are not designed to protect against STI. Men and women who wish to protect themselves from STI should use a condom with every act of intercourse. Only the male condom has been shown to prevent some STIs including HIV. The sexual behaviour of potential users of contraception has relevance to method choice. For example, the IUD is relatively contraindicated for a woman with multiple partners.

LARC is not protective against STIs and HIV. There is some concern that use of hormonal methods of contraception may increase the risk of STIs including HIV.[89] (For more information see relevant chapters.)

WHOMEC advises that for women at risk of STI including HIV, correct and consistent use of condoms is recommended, either alone or with another contraceptive method.

Recommendations:

All health professionals providing contraceptive advice should promote safer sex. [D/GPP]

All health professionals providing contraceptive advice should promote screening for STI when appropriate. [D/GPP]

All health professionals should be able to provide information about local services for STI screening, investigation and treatment. [D/GPP]

Women using LARC should be encouraged to also use condoms with a new partner. [D/GPP]

Table 3.1 Current use of contraception by age

Table 1 **Current use of contraception by age**

Women aged 16–49 *Great Britain: 2003/04*

Current use of contraception	Age 16–17	18–19	20–24	25–29	30–34	35–39	40–44	45–49	All 2003/04	2002/03	2001/02	2000/01	1999/2000	1998/99	1997/98
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Non-surgical															
Pill*	26	58	49	40	31	15	12	5	25	25	28	25	26	26	26
Minipill	*1*	*14*	*9*	*6*	*4*	*4*	*5*	*2*	*5*	*5*	*5*	*5*	*5*	*5*	*5*
Combined pill	*20*	*29*	*31*	*31*	*24*	*10*	*6*	*2*	*17*	*18*	*21*	*17*	*18*	*19*	*19*
Male condom	33	36	37	24	24	22	15	14	23	20	21	21	23	21	21
Withdrawal	3	-	1	3	5	5	1	1	3	3	4	3	5	6	4
IUD	2	-	1	3	5	5	5	4	4	5	3	5	4	4	4
Injection/implant	3	2	6	5	4	3	1	1	3	3	3	3	3	2	2
Safe period/ rhythm method/ Persona	-	-	1	1	2	1	1	0	1	1	2	1	2	2	2
Cap/ diaphragm	-	1	0	0	1	1	1	2	1	1	1	1	1	1	2
Foams/ gels	-	-	-	-	0	0	-	1	0	0	0	0	0	1	0
Hormonal IUS	-	-	0	1	1	1	1	1	1	1	1	1	1	0	0
Female condom	-	-	-	-	0	0	-	-	0	0	0	0	0	0	0
Emergency Contraception†	5	4	2	0	0	0	-	-	1	1	1	1			
Total at least one method non-surgical	50	70	75	66	63	48	35	28	52	51	53	51	54	50	52
Surgical															
Sterilised	-	1	2	3	5	17	17	25	11	11	10	11	12	12	11
Partner sterilised	-	-	1	4	9	15	25	20	12	12	12	11	11	12	10
Total at least one method	50	71	78	73	77	80	77	73	75	74	75	73	76	75	74

* Includes women who did not know the type of pill used.

† Category included for the first time in the 2000/01 questionnaire.

** In 2001/02 this category was changed to 'No method used – no sexual relationship with someone of the opposite sex', prior to this the category was 'No method used – no sexual relationship'.

†† Category included only in 1999/2000 questionnaire and earlier surveys.

*** Percentages sum to more than 100 as respondents could give more than one answer.

1

Table 3.2 Percentage of women experiencing an unintended pregnancy during the first year of typical use, and the first year of perfect use of contraception, and the percentage continuing use at the end of the first year. United States [83]

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use	
Method (1)	**Typical Use**[1] (2)	**Perfect Use**[2] (3)
No method[4]	85	85
Spermicides[5]	29	15
Withdrawal	27	4
Periodic abstinence	25	
Calendar		9
Ovulation method		3
Sympto-thermal[6]		2
Post-ovulation		1
Cap[7]		
Parous women	32	26
Nulliparous women	16	9
Sponge		
Parous women	32	20
Nulliparous women	16	9
Diaphragm[7]	16	6
Condom[8]		
Female (Reality)	21	5
Male	15	2
Combined pill and minipill	8	0.3
Evra patch	8	0.3
NuvaRing	8	0.3
Depo-Provera	3	0.3
Lunelle	3	0.05
IUD		
Progestasert (progesterone T)	2	1.5
ParaGard (copper T)	0.8	0.6
Mirena (LNG-IUS)	0.1	0.1
Spermicides[5]	29	15
Norplant and Norplant-2	0.05	0.05
Female sterilization	0.5	0.5
Male sterilization	0.15	0.10

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Nelson A, Cates W, Guest F, Kowal D. Contraceptive Technology: Eighteenth Revised Edition. New York NY: Ardent Media, 2004.

Table 3.3 Percentage of women continuing use at the end of the first year. United States [83]

Method (1)	% of Women Continuing Use at One Year[3]
No method[4]	
Spermicides[5]	42
Withdrawal	43
Periodic abstinence	51
Calendar	
Ovulation method	
Sympto-thermal[6]	
Post-ovulation	
Cap[7]	
Parous women	46
Nulliparous women	57
Sponge	
Parous women	46
Nulliparous women	57
Diaphragm[7]	57
Condom[8]	
Female (Reality)	49
Male	53
Combined pill and minipill	68
Evra patch	68
NuvaRing	68
Depo-Provera	56
Lunelle	56
IUD	
Progestasert (progesterone T)	81
ParaGard (copper T)	78
Mirena (LNG-IUS)	81
Norplant and Norplant-2	84
Female sterilization	100
Male sterilization	100
Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[9] **Lactational Amenorrhea Method**: LAM is a highly effective, *temporary* method of contraception.[10]	

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Nelson A, Cates W, Guest F, Kowal D. Contraceptive Technology: Eighteenth Revised Edition. New York NY: Ardent Media, 2004.

1 Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides, withdrawal, periodic abstinence, the diaphragm, the male condom, the pill, and Depo-Provera are taken from the 1995 National Survey of Family

Growth corrected for underreporting of abortion; see the text for the derivation of estimates for the other methods.

2 Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. See the text for the derivation of the estimate for each method.

3 Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

4 The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

5 Foams, creams, gels, vaginal suppositories, and vaginal film.

6 Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

7 With spermicidal cream or jelly.

8 Without spermicides.

9 The treatment schedule is one dose within 120 hours after unprotected intercourse, and a second dose 12 hours after the first dose. Both doses of Plan B can be taken at the same time. Plan B (1 dose is 1 white pill) and Preven (1 dose is 2 blue pills) are the only dedicated products specifically marketed for emergency contraception. The Food and Drug Administration has in addition declared the following 17 brands of oral contraceptives to be safe and effective for emergency contraception: Ogestrel or Ovral (1 dose is 2 white pills), Alesse, Lessina, or Levlite, (1 dose is 5 pink pills), Levlen or Nordette (1 dose is 4 light-orange pills), Cryselle, Levora, Low-Ogestrel, or Lo/Ovral (1 dose is 4 white pills), Tri-Levlen or Triphasil (1 dose is 4 yellow pills), Portia or Trivora (1 dose is 4 pink pills), Aviane (one dose is 5 orange pills), and Empresse (one dose is 4 orange pills).

10 However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

3.12 User autonomy and consent

The law and policy governing access to contraception is well developed in the UK, in that all women have had access to free contraception since 1974 via a number of providers.[90][EL=4] Not all methods are available to all women equally as a result of regional variation.

Globally, reproductive rights are not always recognised, leading to statements such as:

"Reproductive rights rest on the recognition of basic rights of couples and individuals to decide freely and responsibly the number and spacing and timing of their children and to have the information to do so, and the right to attain the highest standard of sexual and reproductive health." (para 95, Beijing Platform for Action, 1995)[91]

Reproductive and sexual health care including family planning services and information is recognised as a key intervention for improving the health of women and children, but also as a human right. Right to access, choice and benefit of scientific progress (evidence-based information)are considered important in making an informed choice of contraceptive methods.[16]

For the process of seeking consent to be meaningful, refusal of treatment needs to be one of the patient's options. Competent adults are entitled to refuse treatment even when the treatment would clearly benefit their health. Ethical guidance for obtaining consent, points of law and model documentation are available in the above guidance.[92-95][EL=4]

Recommendation:
Women (couples) should have freedom of choice in contraceptive methods. [D/GPP]

3.13 The law relating to contraception for special groups

Adolescents

Young people aged 16 and 17 are generally presumed to have the ability to consent to their own medical treatment, including contraceptive treatment. Health professionals can provide contraceptive advice and treatment to a young person under the age of 16 without parental involvement if the young person is judged to understand the advice provided and its implications, and her/his physical or mental health would otherwise be likely to suffer, and so provision of advice or treatment is in their best interest.[96]

It is considered to be good practice to follow the criteria outlined by Lord Justice Fraser in the case of Gillick versus West Norfolk and Wisbech Area Health Authority (AHA) and the Department of Health and Social Services (DHSS) when deciding whether a patient under 16 is competent to consent to treatment. These criteria (known as the Fraser guidelines or 'Gillick competence') are that:

- the young person will understand the professional's advice;
- the young person cannot be persuaded to inform their parents;
- the young person is likely to begin, or to continue having, sexual intercourse with or without contraceptive treatment;
- unless the young person receives contraceptive treatment, their physical or mental health, or both, are likely to suffer;
- the young person's best interests require them to receive contraceptive advice or treatment with or without parental consent.

The consent of a competent young person cannot be overruled by a parent. If a person under the age of 18 refuses to consent to treatment, it is possible in some cases for their parents to overrule their decision, though this is generally very rare. This right can only be exercised on the basis that the welfare of the young person is paramount. In this context welfare does not simply mean their physical health. The psychological effect of having the decision overruled

would have to be taken into account and this option would normally only be pursued when the young person was thought likely to suffer 'grave and irreversible mental or physical harm' as a result of their refusal to consent to treatment.[97]

Young people under the age of 16 have as great a right to confidentiality as any other patient. If someone under 16 is not judged mature enough to consent to treatment, the consultation itself can still remain confidential unless there are exceptional circumstances which suggest that the young person's health, safety or welfare is at risk. In this case local child protection procedures should be followed.[98]
(http://www.dh.gov.uk/assetRoot/04/06/72/04/04067204.pdf)

The Mental Capacity Act 2005, which is expected to be implemented in 2007, will define what is meant by capacity and clarify the law on who can make decisions on behalf of people judged to lack capacity.

The FFPRHC provides guidance on contraceptive choices for young people, [99] and DH guidance for health professionals on the provision of contraceptive services for under 16s. [100]

People with learning difficulties

People over the age of 16 are usually regarded as competent to decide their own treatment unless demonstrated otherwise. This applies to people with learning disabilities as much as any other person. It should not be assumed that adults or children are unable to make decisions about their own treatment simply because they have a learning disability. A key factor in assessing the a person's ability to give consent is whether she/he can understand and weigh up the information needed to make the decision about contraceptive treatment. If information is presented in an appropriate way (for instance using simple language or pictorial aids) many people with learning disabilities will be able to consent to their own treatment. The involvement of specialists from learning disability teams or speech or language therapists can be helpful in

assessing the individual's capacity to give consent to treatment though the patient's right to confidentiality should be borne in mind before involving anyone else.[96;101]

Currently no-one else can give consent on behalf of an adult who is not judged to have the capacity to make a decision on their own behalf. However, health professionals may treat the person if it would be in their best interests to do so. The High Court has ruled that 'best interests' go further than the medical interests of the person to include factors such as their general well-being and quality of life, their relationships with people close to them, and their religious or spiritual beliefs. Although the health professional is legally responsible for deciding what is in the patient's 'best interests', any decision should ideally reflect the views of the individual's family, carers or friends. Any decision must be guided by what is genuinely in the best interest of the individual and not what would make life easier for their family or carers. Where there is serious disagreement between health professionals and a patient's family that cannot be resolved, an application may be made to the High Court.[102]
(http://www.dh.gov.uk/assetRoot/04/01/91/59/04019159.pdf)

The Mental Capacity Act 2005, which is expected to be implemented in 2007, will define what is meant by capacity and clarify the law on who can make decisions on behalf of people judged to lack capacity.

People with physical disability

There is a tendency to assume incorrectly that men and women with physical disabilities are not sexually active and have no need of contraception. People with learning and physical disabilities have the same right to information and help with contraception as non-disabled people. Physical disabilities may influence the acceptability, safety and appropriateness of certain methods of contraception. A woman with a disability which makes dealing with monthly menstruation and sanitary protection difficult may appreciate a method which is associated with amenorrhoea. Combined

hormonal contraception (CHC) may be less safe for a woman confined to a wheelchair, since immobilisation is associated with an increased risk of venous thromboembolism and so is CHC. Insertion of an IUD, and the need to check the threads regularly, may prove difficult for some women with a disability. These factors need to be taken into consideration when discussing contraception with women with disabilities.

Recommendations:

People with learning and/or physical disabilities should be supported in making their own decisions about contraception through referral to GPs or specialist clinics. [D/GPP]

Contraception should be seen in terms of the needs of the individual rather than in terms of relieving the anxieties of carers and relatives. [D/GPP]

Where a person with a learning disability is unable to understand and take responsibility for decisions about contraception, carers and other involved parties should meet to address issues around contraceptive need and to establish a care plan for future support of the individual. [D/GPP]

Health professionals should be aware of the law relating to the provision of contraception for young people and for people with learning disabilities. [D/GPP]

3.14 Training of health professionals in contraceptive care

Medical and nurse training are, for the most part, delivered separately. The gold standard basic competency-based training for doctors in the provision of basic sexual and reproductive healthcare, which includes contraception, is the Diploma of the Faculty of Family Planning and Reproductive Health (DFFP). The DFFP includes the provision of some of the long acting methods of contraception and is currently held by approximately 10,000 doctors in the UK,

many working in general practice. Additional competency-based training is required to obtain the qualifications for the provision of intrauterine methods (IUD and IUS) and for subdermal methods of contraception. These qualifications are also awarded by the Faculty of Family Planning and are known as *Letters of Competence in Intrauterine Techniques* and *Subdermal Techniques* respectively. All Faculty qualifications are recertifiable on a 5 yearly cycle. The Membership of the Faculty of Family Planning (MFFP) is specific to the field of Sexual and Reproductive Health and is obtained through examination similar to other College memberships.

The structure of nurse education has changed and many of the old, validated courses are about to or have now expired. In the past, the National Boards had responsibility for standards and curricula for training and though these were variable there was some standardisation and recognition within family planning and contraception. In the ensuing reorganization, Scotland, Wales and Northern Ireland replaced their national boards but England did not. Standards are now the remit of the Nursing and Midwifery Council (NMC), but curricula and course structure is delegated to individual higher education institutes. This has meant that training in family planning and contraception has been addressed in different ways according to the set up within individual universities. For example, it may be part of degrees in general practice, sexual health or women's health or as stand alone modules in contraception, reproductive or women's health. In 2004 the RCN published a Sexual Health Competency framework which was developed in partnership with a number of organisations. This framework is designed to act as a template which reflects the levels of competency expected, from registered practitioner through to consultant practitioner levels, and should help to underpin training in the future.[103] The RCN recommends that all nurses working in general practice, family planning, contraception and genito-urinary (GU) clinics should undertake a two day Sexually Transmitted Infections Foundation course (STIF), and that family planning and GU-trained nurses should regularly update their knowledge and skills to maintain their competence to practise. Training guidance is available from the RCN for nurses working in this field in the following areas: contraception and sexual health in primary care,[104] fitting

intrauterine devices,[105] and inserting and/or removing subdermal implants.[106] Details of these are available from www.rcn.org.uk. An RCN accredited Sexual Health Skills distance learning programme has recently been developed. It is aimed at nurses who want a holistic foundation in sexual health but who may not specialise in this field. The course is validated by the University of Greenwich.

A survey undertaken by the Contraceptive Education Service run by the Family Planning Association and Health Education Authority identified that 88% of GPs had some training in family planning but two thirds had family planning qualifications issued in the 1970s.[107] Just 12% had recent training with practice nurses more likely to have attended update training courses. There is no training data available for health professionals working in community contraceptive services. However, job descriptions for staff grade, associate specialist and consultants specify that candidates should hold either the diploma or membership of the Faculty of Family Planning or an equivalent qualification with evidence of recertification if appropriate.

For nurses working within community contraceptive services, a recognised family planning qualification or equivalent is required. Training for both nurses and doctors involves a theoretical component and practical placement. Doctors training in GU Medicine now need to obtain the DFFP as part of their specialist registrar training but, in Obstetrics and Gynaecology, candidates for the membership examination are just required to receive instruction at eight family planning clinics. There is no requirement by the RCOG for specialist registrars to attend a DFFP theory course, which is regrettable, as the level of contraceptive knowledge amongst trainees is often poor.

Most of the practical, hands-on training takes place in community contraceptive services but, with pressure from increasing patient attendances and referral of complex medical cases, training resources are stretched to their limits.

Further obstacles to maintaining, let alone increasing, practical placement numbers include poor terms and conditions of employment for senior doctors

who are leaving or returning to general practice. In addition, the following are also significant barriers to expanding medical training:

- poor support and funding of training by the postgraduate deaneries
- as training develops from an educational perspective, this requires trainers to spend more time with trainees developing and assessing competency-based, learning objectives

These issues need to be discussed as a matter of urgency locally, regionally and nationally so that the future workforce is adequately equipped to provide level one services in primary care and accurate contraceptive advice in secondary care.

Recommendations:

All health professionals advising women about contraceptive choices should be competent to:

- **assist women to consider and compare the risks and benefits of all methods relevant to their individual needs**
- **manage common side effects. [D/GPP]**

All health professionals providing contraceptive care should ensure that they have an agreed mechanism in place for referring women for LARC if they do not provide LARC within their own practice/service. [D/GPP]

All health professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. [D/GPP]

3.15 Cost-effectiveness of LARC methods versus other reversible contraceptive methods

The economic analysis undertaken for this guideline demonstrated that all LARC methods are associated with a smaller number of pregnancies compared to the male condom and the COC, for all time horizons considered

in the economic model, i.e. up to 15 years of contraceptive use. For one year of use, IUD and the injectable dominate male condom as well as COC (i.e. IUD and the injectable are less costly and more effective than male condom and COC). The implant is more effective and more costly than male condom and COC for one year of use, incurring an additional cost equal to £378 and £405 per pregnancy averted, respectively. For the same time-frame, IUS is also more effective and more costly than male condom and COC, at an additional cost of £437 and £513 per pregnancy averted, respectively. For periods of contraceptive use equal to 2 years and above, all LARC methods dominate male condom and COC.

Evidence statement

- **LARC methods are more cost-effective compared to male condom and COC, even for short periods of contraceptive use (1- 2 years).**

Recommendation:

LARC methods should be available in the NHS, since they are cost effective compared with other reversible contraceptive methods commonly used.

3.16 Brief overview of features common to progestogen only methods

This guideline discusses four methods of LARC, the copper IUD and the progestogen only methods. There are common features of progestogen only contraception regardless of dose and route of administration. The Guideline Development Group felt that a brief overview of the major effect of progestogens on various systems would be a useful introduction to the specific chapters.

Contraception can be broadly divided into two large categories, hormonal and non-hormonal. There are two categories of hormonal contraception, combined (estrogen plus progestogen) and progestogen only. Included in the category

of LARC are the copper intrauterine device and three progestogen only methods of contraception (injectables, implants and the intrauterine system).

Long acting delivery systems have the theoretical advantage of providing very constant release rates of steroid hormone (compared with daily administration) and also avoid the first pass effect through the liver, enabling lower doses of steroids to be used. However, the injectable preparations deliver a higher dose of hormone, while the oral preparation, implants and intrauterine systems deliver much lower doses.

Mode of action

The mode of action depends on the dose of hormone. Higher doses (injectables) inhibit follicle development and ovulation completely, alter the characteristics of cervical mucus interfering with sperm transport and cause endometrial changes including atrophy. Intermediate doses (the subdermal implant Implanon) inhibit ovulation but allow follicular development, while very low doses (intrauterine delivery systems and the implants Norplant) inhibit ovulation only inconsistently and rely mainly on their effect on cervical mucus. In addition to the effect on the ovary and cervical mucus, all methods have an effect on the endometrium. The intrauterine system has a very marked effect causing endometrial atrophy and inhibiting implantation.

Side effects

Bleeding disturbances

Progestogen only methods disrupt regular menstrual cycles and the resulting 'bleeding disturbance' is the commonest cause for discontinuation of the method. The mechanism of action of the method determines the predominant bleeding pattern. Bleeding patterns depend on the degree of suppression of ovarian activity. If normal ovulation occurs consistently a woman will experience menstrual bleeds at a frequency characteristic of her normal cycle. If both ovulation and follicle development are completely suppressed,

amenorrhoea will result and many women do experience amenorrhoea while using Depo Provera®. If ovulation or follicular development sufficient to stimulate endometrial growth occur irregularly, bleeding will be erratic and unpredictable (implants) unless there is endometrial atrophy (LNG-IUS) when, regardless of the effect on ovarian activity, amenorrhoea is common. A local effect on the endometrium of the continuous administration of progestogens also probably contributes to the bleeding patterns.

Ovarian cysts

The incomplete suppression of ovarian activity is a recipe not only for erratic bleeding, but also for the development of ovarian follicular cysts. These occur in 20% of women using the LNG-IUS. They are almost always asymptomatic.

The metabolic side effects of progestogens

These are said to be associated with a range of common minor symptoms including acne, hirsutism, headache, mood change and weight gain or bloating. All are common complaints among women not using contraception. Depo Provera may be associated with more significant weight increase than other POC.

Ectopic pregnancy

Ectopic pregnancy is listed in many older textbooks as a side effect of the POC due to the theoretical effect of progestogens on tubal motility. The best data are for Norplant, and show no increased risk compared with women not using contraception. Ectopic pregnancy is discussed in more details in subsequent chapters.

Cancer

In the large meta- analysis reporting a relative risk of 1.24 for use of the COC[108], an increased relative risk of breast cancer for both oral and injectable

progestogen-only methods of contraception (RR 1.17 for both) was demonstrated although for injectables this was not statistically significant. In a review of other pooled analyses[109] no significant associations were found and the author concludes that there are no concerns. There are much fewer data for POP than for COC and women with risk factors for breast cancer may be preferentially prescribed POC. Recent anxieties about the contribution of progestogens to the increased risk of breast cancer associated with HRT have not yet spread to progestogen only contraceptives. There is no evidence for any increased risk of other cancers and indeed some evidence to suggest a reduction in the risk of endometrial cancer.

Cardiovascular disease including venous thromboembolism

There is no evidence for an increase in the risk of stroke, myocardial infarction or VTE in association with POC.[110] An association between VTE and progestogen used for the treatment of gynaecological conditions such as anovulatory dysfunctional uterine bleeding[111] is likely to be due to prescriber bias since the COC - often the method of choice – is contraindicated in women with known risk factors for VTE. A very weak association between use of Norplant and hypertension[112] may be due to observer bias.

A systematic review of 3 cohort studies and 1 cross-sectional study reported no significant association of high blood pressure with the use of progestogen only pills for up to 2-3 years of follow-up. [113][EI=3]

Gall bladder disease

A weak association between use of Norplant and gall bladder disease[112] has been described but there is no evidence of any association with other POC.

Bone Mineral Density

No study has demonstrated any adverse effect of progestogen-only implants on bone mineral density. It is unlikely therefore that use of oral or intrauterine

POC would be harmful. Injectable methods however deliver higher doses of progestogen suppressing ovarian activity and causing hypoestrogenism and loss of bone mineral density and there are concerns that their use may increase the risk of osteoporosis.[114] (Please refer to the forthcoming NICE clinical guideline on Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk) http://www.nice.org.uk/page.aspx?o=33923

Return to fertility

Mean time to pregnancy (TTP) after stopping contraception varied with the preceding contraceptive method and with its duration of use. Return to fertility occurs within days of cessation of all POC methods except injectables. The delay following discontinuation of DMPA is well recognised but pregnancy rates eventually reach those associated with cessation of other methods.

The methods described in the following chapters do not represent an order of recommended priority.

4 Copper intrauterine devices (IUDs)

4.1 Introduction

4.1.1 What they are

Intrauterine devices (IUDs) are small contraceptive devices inserted through the cervix and positioned in the cavity of the uterus. IUDs are the second most commonly used contraceptive in the world (the most common being female sterilisation).[115]

Five copper-containing IUDs are currently available in the UK: T-Safe® CU 380 A (For the purposes of the guideline we have regarded T-Safe Cu 380 as comparable to TCu380A), Multiload® Cu375, Nova-T® 380, Flexi-T® 300, and GyneFix® (details of IUDs in table 4.1). The available IUDs have copper on a plastic frame or a thread (frameless), with a small thread that protrudes through the cervical canal into the upper part of the vagina allowing easy removal. The tails also can be checked regularly by the wearer to ensure correct placement. IUDs vary in structural design and amount of copper. The levonorgestrel-only intrauterine system has some similar features to IUDs and is considered in a separate chapter. (see Chapter 5).
New devices available in 2004 include the Multisafe 375 (similar to Multiload 275), NeoSafe 380 (similar to Nova T 380), and Flexi T 380. (not yet in BNF 2005)

4.1.2 Mechanism of action

IUDs prevent pregnancy by impairing gamete viability at fertilization and they have a strong inhibitory effect on implantation.[116;117] Copper ions provide most if not all of the effects.[116-120][EL=3]

Recommendation:
Women should be advised that there is evidence that all copper IUDs probably act by both impairing gamete viability and inhibiting implantation. [C]

4.1.3 Use in the UK

In 2003/4, it was estimated that 4% of women aged 16-49 years in Great Britain chose the IUD as their preferred method of contraception. [1][EL=3]

4.1.4 Duration of action

The IUDs currently available in the UK are licensed for a variety of time periods from 5 to 8 years. Studies have shown that most of the widely used copper IUDs are effective for at least five years and many are effective for longer.[121;122]

RCT data suggest that the TCu380A appears effective for up to 12 years. A study combined data from two RCTs across 24 centres with a total of 3,277 women and compared the effectiveness of TCu380A and the CuT220 at 8-, 10- and 12-years of use. Pregnancy rates per 100 women were significantly lower for the TCu380A at all time points (2.2 per 100 at 8-, 10- and 12-years). No pregnancies were reported among women using the TCu380A after 8 years of use.[123] The Gyne T380 is no longer available in the UK but women with this device may continue to use it for its 10-year licensed duration.

Multiload versions containing lower amounts of copper (no longer available) were licensed for three years.[121] Results from three randomised trials suggest that the Multiload Cu375 is effective for 5 years. (See 4.2)

The GyneFix is licensed for 5 years.[121] We found no evidence supporting a longer duration of use.

Previous UK practice recommended that a copper IUD inserted at age 40

years or over may be retained beyond the licensed duration until contraception is no longer required.[121;122;124] Although no studies based on IUD devices currently licensed within the UK have been undertaken to support this practice, the GDG supports this recommendation.

Summary of Evidence

- **Women using the TCu380A for up to 12 years had low pregnancy rates (around 2%)**

Recommendation:

Women who are aged 40 and older at the time of copper IUD insertion can retain the device until they no longer require contraception. It is important that this is discussed with women at fitting as it is outside the product license. [D/GPP]

4.1.5 The evidence

In this guideline, we presented evidence from studies of coppers IUDs which are currently licensed and available in the UK: T Safe Cu380A, Multiload Cu375, Nova –T 380, Flexi-T 300 and Gynefix.

In addition to reviewing evidence identified from our search strategy, we assessed studies reviewed in a Health Technology Report [125] and included those studies deemed to be appropriate to the population of UK and the developed countries in terms of body weight and access to contraceptive service provision. (See section 3.4)

4.2 Effectiveness

Framed IUDs

One RCT undertaken in Nigeria (n=200) reported no difference in pregnancy

rates among women using Multiload Cu375 (n=100) compared to women using TCu380A (n=100) (0.0 versus 1.1 per 100 women years at 1 year).[126][EL=1+]

A multicentre RCT reported no difference in pregnancy rates among women using Multiload Cu375 (n=740) compared to women using TCu380A (n=737) (adjusted rates 0.8 versus 0.3 per 100 women years at 1 year, 1.3 versus 0.6 per 100 women years at 2 years and 1.8 versus 0.6 per 100 women years at 3 years).[127;128][EL=1+]

Another RCT reported a significantly higher pregnancy rate in women using Multiload Cu375(n=948) than women using TCu380A (n=946) (adjusted rates 1.4 versus 0.4 per 100 women years at 1 year, 2.7 versus 1.2 per 100 women years at 2 years).[129][EL=1+]

Interim results from a WHO randomized comparative trial reported a significantly higher pregnancy rates among women using Multiload 375 than women using TCu380A at 3 years (2.9 vs 1.6 per 100 women) and at 10 years (5.3 vs 3.4 per 100 women respectively). The total number of women completing 10 years was 727. [130-132][EL=1+]

One RCT (an abstract) compared NovaT380 (n=470) and Gyne T380 Slimline (n=487) and reported significant contraceptive effectiveness at 1 year but not thereafter. The cumulative pregnancy rates were 3.6 vs 1.7 per 100 woman-years at 3 years. Fifty-two percent of Nova-T 380 and 47% of Gyne T 380 completed the 3 years follow-up.[133][El=1-]

A non-comparative study (n=574) in the UK reported a cumulative pregnancy rate of 0.8, 1.6, 2.0, 2.0 and 2.0 among Nova T 380 users at 1, 2, 3, 4 and 5 years respectively.[134][EL=3]

Another non-comparative study (n=400) in Finland reported a cumulative pregnancy rate of 0.5 and 1.6 among Nova T 380 users at 1 and 2 years respectively.[135][EL=3]

Frameless versus framed IUDs

GyneFix is the only frameless copper IUD currently licenced in the UK. Cu-Fix and FlexiGard are frameless copper IUDs similar to GyneFix.

A systematic review of four RCTs [136-139] reported no significant difference in pregnancy rates between the frameless device (Cu-Fix, Flexigard and Gynefix) and TCu380A IUDs at 1 year (RR 1.79; 95% CI 0.81 to 3.95) and 3 years (range of 0.0 to 2.2 vs 0.3 to 1.6)(RR 1.34; 95% CI 0.85 to 2.10). [140][EL=1++] In two of the trials [137;138] included, pregnancy and expulsion rates with the frameless device were higher in the first year when compared with the TCu380A. This may be due to the use of a deficient introducer for the frameless IUDs in the studies.

Summary of evidence

- **Women using the Multiload Cu375 had a higher pregnancy rate (5.3%) when compared with women using TCu380A (3.4%) for up to 10 years.**
- **Women using Nova-T 380 had a pregnancy rate of under 2% for up to 5 years.**
- **There was no significant difference in pregnancy rates between the frameless devices (0 to 2%) and TCu380A (0.3 to 1.6%) after 3 years of use.**

Table 4.1 Copper IUDs: Pregnancy rates

	Pregnancy rates%					
Studies	**TCu380A (licensed 8 years)**	**MLCu375 (licensed 5 years)**	**Frameless (Cu-Fix, Gynefix, Flexigard) (licensed 5 years)**	**Nova-T 380 (licensed 5 years)**	**Rate measured at point (year)**	**EL**
[126]	1.1	0.0			1	1+
[127;128]	0.3	0.8			1	1+
	0.6	1.3			2	
	0.6	1.8			3	
[129]	0.4	1.4			1	1+
	1.2	2.7			2	
[130;131] [132]	1.6	2.9			3	1+
	3.4	5.3			10	
[140]	0.3 to 1.6		0.0 to 2.2		3-6	1++
[134]				0.8	1	3
				2.0	3	
				2.0	5	
[135]				0.5	1	3
				1.6	2	

Recommendations:

Health professionals should be aware that the TCu380A is the copper IUD of choice because of its effectiveness and licenced duration of action of 8 years. [B]

Women should be informed that the pregnancy rate associated with the use of IUDs with 375 mm^2 copper or above is less than 2 in 100 women over a 5-year period. [C]

Copper IUDs versus other contraceptive methods

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a cumulative pregnancy rate of 1.1 and 1.4 per 100 women among LNG-IUS and TCu 380A users respectively at 7 years.[141][EL=1+] Results of this RCT were documented in four other reports during the 7-year study period.[142-146]

Interim results from the WHO international muticentred RCT (n=3815

insertions) reported a significantly higher cumulative pregnancy rate among users of TCu380A IUD when compared with LNG-IUS users at 6 years (2.0 versus 0.5).[131;132][EL=1+]

One RCT compared LNG-IUS (n=141) and Nova T IUD (n=136) (copper surface 200) in Finland and Brazil and reported a pregnancy rate of 0.08/458 women years and 0.6/431 women years respectively at 5 years.[147][EL=1+] Results of this RCT were documented in 3 other reports during the 5-year study period.[148-150]

One European multicentre RCT compared LNG-IUS (n=1821) and Nova T IUD (n=937) (copper surface 200). It reported a significant difference in cumulative pregnancy rate of 0.3% versus 3.7% and 0.5% versus 5.9% in users of IUS-20 and NovaT IUD respectively at 3 and 5 years.[151;152][EL=1+] Results of this RCT were documented in two other reports during the 5-year study period.[153;154]

A cohort study in East Africa compared women using TCu380A (n=343) with women using COC (n=333) and women using DMPA (n=400). There was no difference in pregnancy rates (1.5 versus 2.1 versus 0.3 per 100 women years at 1 year).[155][EL=2-]

Summary of evidence

Table 4.2 Copper IUDs vs LNG-IUS: pregnancy rates %

	Pregnancy rates%				
Studies	**TCu380A (licensed 8 years**	**Nova-T 200 (not licensed)**	**LNG-IUS (licensed 5 years)**	**Rate measured at point (year)**	**EL**
153 154		3.7	0.3	3	1+
		5.9	0.5	5	1+
148 149 150		<0.5	< 0.5	5	1+
131 132	2.0		0.5	6-7	1+
142 143 144	1.4		1.1	7	1+

- **Although there is some evidence to suggest that the IUS may be more effective than a copper IUD containing 380mm^2 copper, the difference is very small and of doubtful clinical significance.**
- **There was insufficient evidence to make a recommendation for the comparison of effectiveness between currently available copper IUDs and other contraceptive methods.**

4.3 Expulsion

Expulsion of an IUD occurs in approximately 1 in 20 women, and is most common in the first three months after insertion. Expulsion commonly occurs during menstruation.[118][EL=4]

Copper IUDs

RCTs comparing the TCu380A to MLCu375 reported expulsion rates ranging from 3.3% to 6% at 1 year, 4.5% to 6.7% at 2 years, 5.4% at 3 years and 11.2% at 10 years among TCu380A users vs 0 to 4% at 1 year, 5% at 2 years, 6.5% at 3 years and 14.8% at 10 years among MLCu375 users [126-132][EL = 1+]

A systematic review of four RCTs [136-139] reported a significant higher expulsion rate with the frameless IUD when compared with TCu380A at 1 year (RR 2.48; 95% CI 1.89 to 3.26). It was suggested that this could be due to the use of a deficient introducer for the frameless IUD. Retention of the frameless device also appeared to depend on the skill and dexterity of the clinician during insertions, despite the kind of introducer used. The cumulative net expulsion rates for the two groups were similar from two to six years (3.6% with Flexigard vs 2.6% with TCu380A)(RR 1.20; 95% CI 0.79 to 1.84). Nulliparous women were excluded in three of the studies reviewed.[140][EL=1++]

We did not identify any studies which compared Nova T380 with other IUDs.

A non-comparative study (n=574) in the UK reported cumulative discontinuation rates due to expulsion of 6.0, 8.6, 10.3, 12.3 and 13.0 among Nova T 380 users at 1, 2, 3, 4 and 5 years respectively.[134][EL=3]

Another non-comparative study (n=400) in Finland reported cumulative discontinuation due to expulsion was 1.6 and 2.8 among Nova-T 380 users at 1 and 2 years. [135][EL=3]

Summary of evidence

- **The expulsion rates are lower with TCu380A than MLCu375 at 3 years (5.4% vs 6.5%) and at 10 years (11.2% vs 14.8%).**
- **The expulsion rates between TCu380A (2.6%) and frameless IUDs (3.1%) are similar between two and six years.**

Summary of evidence

Table 4.3 Copper IUDs: expulsion rates %

	Expulsion rates %					
Studies	**TCu380A (licensed 8 years)**	**MLCu375 (licensed 5 years)**	**Frameless (Cu-Fix, Gynefix, Flexigard) (licensed 5 years)**	**Nova-T 380 (licensed 5 years)**	**Rate measured at point (year)**	**EL**
[126] [128] [127] [129;130]	3.3 to 6.0	0.0 to 4.0			1	1+
	4.5 to 6.7	5			2	
	5.4	6.5			3	
[131;132]	11.2	14.8			10	1+
[140]	2.6		3.1		3-6	1++
[134]				6.0	1	3
				10.3	3	
				13.0	5	
[135]				1.6	1	3
				2.8	2	

Copper IUDs versus LNG-IUS

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu380A users in discontinuation rate due to expulsion (6.0% versus 5.5%, 7.3%

versus 6.1%, 11.8% versus 7.4% and 11.8% versus 8.4% at 1, 2 , 5 and 7 years respectively).[141-145][EL=1+]

Interim results from the WHO international multicentred RCT (n=3815 insertions) reported no significant difference between LNG-IUS users and TCu380A IUD users in discontinuation rates due to expulsion (7.5% versus 8.2%) after 6 years.[131;132][EL=1+]

An RCT compared LNG-IUS (n=141) and Nova T IUD (n=136)(copper surface 200) in Finland and Brazil. It reported cumulative discontinuation rates due to expulsion of 0.6% versus 4.5%, 0.6% versus 6.1% and 2% versus 6% at 1, 2 and 5 years respectively).[147-150][EL=1+]

One European multicentre RCT which compared LNG-IUS (n=1821) and Nova T IUD (n=937) (copper surface 200) reported cumulative rates for removal due to expulsion of 3.4% versus 3.4%, 4.2% versus 4.1%, 4.8% versus 4.8%, 4.9% versus 5.3% and 4.9% versus 5.5% at 1, 2, 3, 4, and 5 years respectively.[151-154][EL=1+]

Summary of evidence

Table 4.4 Copper IUDs vs LNG-IUS: expulsion rates %

	Expulsion rates%				
Studies	**TCu380A (licensed 8 years)**	**Nova-T 200 (not licensed)**	**LNG-IUS (licensed 5 years)**	**Rate measured at point (year)**	**EL**
153 154		3.4	3.4	1	1+
		4.8	4.8	3	
		5.5	4.9	5	
148 149 150		6.0	2.0	5	1+
131 132	8.2		7.5	6-7	1+
142 143 144	5.5		6.0	1	1+
	6.1		7.3	2	
	7.4		11.8	5	
	8.4		11.8	7	

- **The expulsion rates between LNG-IUS and TCu380A varied, from 7.5% vs 8.2% after 6 years. One study reported an expulsion rate of 11.8% vs 8.4% at 7 years.**

Recommendations:
Women should be advised that an IUD may be expelled but that this occurs in fewer than 1 in 20 women over a 3-year period. [C]

Women should be instructed how to check for the presence of the IUD threads and advised to do so regularly with the aim of recognising expulsion. [D/GPP]

4.4 Discontinuation and reasons for discontinuation

Framed IUDs

Altered bleeding and altered bleeding with pain are the most common reasons cited for requesting IUD (Nova T and Nova-T 380) removal.[118;134] One RCT comparing the TCu380A to MLCu375 reported similar rates for overall discontinuation rates (9.5 vs 8.4% and 14.5 vs 15% at 1 and 2 years). In this study, the discontinuation rates due to bleeding and pain were 14 vs 10% and 19 vs 14% at 1 and 2 years.[129][EL=1+]

Another RCT comparing the TCu380A to MLCu375 reported similar rates for overall discontinuation rates (10 vs 12%, 20 vs 23% and 33 vs 39% at 1, 2 and 3 years). In this RCT, the discontinuation rates due to bleeding and pain were 5 vs 4%, 8 vs 8% and 9 vs 11% at 1, 2 and 3 years. [127][EL=1+]

Overall discontinuation rates were reported to be 14.2 vs 13% among users of TCu380A and MLCu375 respectively at 1 year. In this RCT, discontinuation due to PID was reported to be 1.2% vs 1% at 1 year.[126][EL=1+]

Interim results from a WHO RCT reported similar overall discontinuation rates between users of TCu380A to MLCu375 at 12 vs 11%, 22 vs 22% and 60 vs

63% at 1, 3 and 10 years). Discontinuation due to PID was 0.4 vs 0.5% at 10 years. [130-132][EL=1+]

Frameless IUDs

A systematic review of 4 RCTs reported no significant difference in discontinuation rate between frameless IUDs and TCu380A at 3 years (10-29% vs 15-27%)(RR 0.94; 95% CI 1.00 to 1.13).There was no significant difference in removal rates due to excessive bleeding and /or pain among parous women who used either the frameless copper IUDs (Cu-Fix, FlexiGard and GyneFix) or the TCu380A (~7% vs 8%)(RR 0.92, 95% CI 0.74 to 1.14). No differences were identified in rates of removal for pain alone between the two groups (1% vs 2%)(RR 0.60; 95% CI 0.34 to 1.05). There was no significant difference in removal due to PID (0.1% with frameless vs 0.4% with TCu380A at 3 years (RR 0.80; 95% CI 0.23 to 2.81). Only one perforation with Gynefix was reported in these 4 RCTs.[140][EL=1++]

A non-comparative study (n=574) in the UK reported a cumulative discontinuation rate for all reasons of 26.2, 40.7, 53.0, 62.5 and 67.5 among Nova T 380 users at 1, 2, 3, 4 and 5 years respectively; the corresponding cumulative discontinuation due to bleeding problems were 10.3, 16.2, 21.1, 26.5 and 29.6; due to pain (1.9, 3.4, 4.5, 5.5 and 7.1) and due to PID (0.9) throughout the 5 years.[134][EL=3]

Another non-comparative study (n=400) in Finland reported a cumulative discontinuation rate of 11.0 and 24.5 among Nova T 380 users at 1 and 2 years respectively; the corresponding cumulative discontinuation rate due to bleeding problems was 4.7 and 8.7, and due to pain (1.3 and 2.3) at 1 and 2 years respectively.[135][EL=3]

Summary of evidence

Table 4.5 Copper IUDs: discontinuation rates %

	Discontinuation rates%						
Studies	**Reasons for removal**	**TCu380A (licensed 8 years**	**MLCu375 (licensed 5 years**	**Frameless (Cu-Fix, Gynefix, Flexigard) (licensed 5 years**	**Nova-T 380 (licensed 5 years**	**Rate measured at point (year)**	**EL**
[129]	**Overall**	9.7	8.4			1	1+
		14.5	15			2	
[127]		10	12			1	1+
		20	23			2	
		33	39			3	
[130] [131] [132]		12	11			1	1+
		22	22			3	
		60	63			10	
[140]		15 to 27		10 to 29		3	1++
[134]					26	1	3
					53	3	
					68	5	
[135]					11	1	3
					25	2	
[18374}	**Bleeding and pain**	5	4			1	1-
		8	8			2	
		9	11			3	
[129]		14	10			1	
		19	14			2	
[127]		5	4			1	1+
		8	8			2	
		9	11			3	
[140]		8.0		7.0		3-6	1++
[134]					10	1	3
					21	3	
					30	5	
[135]					4.7	1	3
					8.7	2	
[131] [132]	**PID**	0.4	0.5			10	1+
[126]		1.2	1.0			1	1-
[129]		1.3	0.6			2	
[127] {17654]		7.0	4.6			3	1-
[140]		0.4		0.1		3-6	1++
[134]					0.9	5	3

- **The discontinuation rate for all reasons is similar between different copper IUDs. Over 5 years of use, between 1 in 4 and 1 in 2 women will stop using the method.**

- **The discontinuation rate for all reasons is similar between frameless and the TCu380A (below 30% at 3 years). Discontinuation rate is also similar due to bleeding and pain (around 8% at 3 years).**

- **The commonest side effect that leads to discontinuation of copper IUDs is bleeding problems.**

Copper IUDs versus LNG-IUS

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a significantly difference in cumulative discontinuation rate between LNG-IUS users and TCu380A users (24% versus 18%, 40% versus 31%, 51% versus 41%, 59% versus 52%, 67% versus 60% and 77% versus 72% at 1, 2, 3, 4, 5, and 7 years respectively). There were significant differences in cumulative discontinuation rates due to amenorrhoea (4.9% versus 0.1%, 8.4% versus 0.2%, 19.7% versus 0.4% and 24.6% versus 1.1% at 1, 2, 5 and 7 years respectively). The annual discontinuation rate due to amenorrhoea ranged from 2.5% to 6.6 % in the first 5 years. The cumulative discontinuation rates due to other menstrual problems and pain were not significantly different at 1 and 2 years (6.0% versus 7% and 8.6% versus 11.3% respectively) but were significantly different at 5 and 7 years (15.4% versus 23% and 20.4% versus 30% respectively). There were no significant differences between the 2 groups in discontinuation rate due to PID (0.9% versus 0.8% ,1.4% versus 1.2%, and 1.6% versus 1.5% at 1-2 ,3-5 and 6-7 years respectively).[141-145][EL=1+]

Interim results from the WHO international multicentred RCT (n=3815 insertions) reported a significant difference in discontinuation rates due to bleeding problems between LNG-IUS users (n=464) and TCu380A IUD users (n=580) at 6 years (36% versus 11%). There were significant differences in discontinuation rates due to amenorrhoea (23.5% versus 0.5%), reduced bleeding (10.9 versus 3.1) and increased bleeding (5.4% versus 7.2%) in the

two groups at 6 years. There was no significant difference in discontinuation rates due to PID (0.3% versus 0.1%) at 6 years.[131][EL=1+]

An RCT which compared IUS-20 (n=141) and Nova T IUD (n=136)(copper surface 200) in Finland and Brazil reported cumulative discontinuation rates of 16% versus 14%, 33% versus 28% and 45% versus 50% at 1, 2 and 5 years respectively. There was a significant difference in the cumulative discontinuation rates due to amenorrhoea in the two groups (2.6% versus 0%, 10.7% versus 0% and 13% versus 0% at 1, 2 and 5 years respectively). The data for the cumulative discontinuation rates due to other menstrual problems and pain were 6.5% versus 3.5%, 7.5% versus 7.1% and 8.3% versus 21.7% at 1, 2 and 5 years respectively.[147-150][EL=1+]

One European multicentre RCT which compared IUS-20 (n=1821) and Nova T IUD (n=937) (copper surface 200) reported discontinuation rates of 20% versus 17%, 34% versus 29%, 43% versus 41%, 49% versus 49% and 53% versus 56% at 1, 2, 3, 4 and 5 years. The cumulative rate for removal due to amenorrhoea was significantly higher in users of IUS-20 than Nova T (1.5% versus 0%, 2.9% versus 0%, 3.6% versus 0%, 4.2% versus 0% and 4.3% versus 0% at 1, 2, 3, 4 and 5 years). The cumulative rate for removal for other bleeding problems and pain were 7.4% versus 7.3%, 11.1% versus 11.6%, 13% versus 15.3%, 14.2% versus 18.1% and 15.1% versus 20.4% at 1, 2, 3, 4 and 5 years respectively. The cumulative rates for removal due to PID were 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5%, and 0.6% versus 1.6% respectively. Significant differences were also reported in removal rates between IUS and IUD due to depression (2.9% versus 0%), acne (2.3% versus 0.4%), headache (1.9% versus 0.25) and weight change (1.5% versus 0%) at 5 years.[151-154][EL=1+]

Summary of evidence

Table 4.6 Copper IUDs vs LNG-IUS: discontinuation rates %

		Discontinuation rates %				
Studies	**Reasons for removal**	**TCu380A (licensed 8 years)**	**Nova-T 200 (not licensed)**	**LNG-IUS (licensed 5 years)**	**Rate measured at point (year)**	**EL**
[153] [154]	**Overall**		17	20	1	1+
			41	43	3	
			56	53	5	
[148] [149] [150]			14	16	1	1+
			28	33	2	
			50	45	5	
[142] [143] [144]		18		24	1	1+
		41		51	3	
		67		60	5	
		72		77	7	
[153] [154]	**Amenorrhoea**		0.0	1.5	1	1+
			0.0	3.6	3	
			0.0	4.3	5	
[148] [149] [150]			0.0	2.6	1	1+
			0.0	10.7	2	
			0.0	13	5	
[142] [143] [144]		0.1		4.9	1	1+
		0.2		8.4	2	
		0.4		19.7	5	
		1.1		24.6	7	
[131] [132]		0.5		23.5	6-7	1+
[153] [154]	**Bleeding and pain**		7.3	7.4	1	1+
			15.3	13	3	
			20.4	15.1	5	
[148] [149] [150]			3.5	6.5	1	1+
			7.1	7.5	2	
			21.7	8.3	5	
[142] [143] [144]		7.0		6.0	1	1+
		11.3		8.6	2	
		23.0		15.4	5	
		30.0		20.4	7	
[131] [132]		11.0		36.0	6-7	1+
[153] [154]	**PID**		0.4	0.3	1	1+
			1.5	0.5	3	
			1.6	0.6	5	
[142] [143] [144]		0.8		0.9	1-2	1+
		1.2		1.4	3-5	
		1.5		1.6	6-7	
[131] [132]		0.1		0.3	6-7	1+

- **The overall discontinuation rate was over 60% for both IUD and IUS users at 5 years.**

- **Discontinuation due to amenorrhoea was about 25% at 5 years among LNG-IUS users, 1% in IUD users at 5-6 years.**
- **Discontinuation due to bleeding/pain was about 16% in LNG-IUS users and 24% in IUD users at 5 years.**
- **The rate for discontinuation due to PID was under 1% at 5-6 years.**

Recommendation:
Health professionals and women should be made aware that up to 50% of women will stop using the IUD within 5 years. The most common reason for discontinuation is unacceptable vaginal bleeding. [C]

4.5 Adverse effects

4.5.1 Bleeding problems

(See 4.4 discontinuation rates)

It has been reported that although IUDs do not affect ovulation, the onset of menstrual bleeding occurs earlier than normal cycles.[156]

Copper IUDs

One RCT reported no difference in the rates of menorrhagia (4% versus 5% among users of TCu380A (n=100) and MLCu375 (n=100) 1 year after IUD insertion. The corresponding rates for amenorrhoea were 2% versus 2%, for intermenstrual bleeding (6% versus 4%) and for dysmenorrhoea (27% versus 24%).[126][EL=1+]

Another RCT reported no difference in the rates of hospitalization for heavy menstrual bleeding (0.3% versus 0.3%) among users of TCu380A (n=737) and MLCu375 (n=740) at 1 year. In this study the rate for intermenstrual bleeding (not requiring hospitalization) was 8.3% versus 9.7%, and for dysmenorrhoea 48.6 versus 44.5.[128][EL=1+]

Summary of evidence

- **IUD use is associated with increased bleeding problems and dysmenorrhoea but one year after insertion there is no significant difference in the rates of problems comparing TCu380A, MLCu375 and MLCu380.**

Recommendation:

Health professionals and women should be made aware of the risk of heavier bleeding and/or dysmenorrhea with IUD use. [C]

Copper IUDs versus other contraceptive methods

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported that LNG-IUS (n=1125) users were more likely to experience amenorrhoea than TCu380A IUD users (n=1121) at 3 months (RR 2.15; 95% CI 1.31 to 3.56) and at 3 years (RR 7.24; 95% CI 4.14 to 12.65). No significant differences were noticed between the two groups in terms of prolonged bleeding at 3 months and 1 year. For LNG-IUS users, amenorrhoea, spotting, menorrhagia, dysmenorrhoea and premenstrual syndrome all occurred at a significant higher incidence in the first 2 years after insertion than at 3 and 4 years. The incidence of these bleeding disturbances declined further at 6 years and later years. Women aged 30 or over using LNG-IUS were significantly less likely to complain of amenorrhoea, oligoamenorrhoea and dysmenorrhoea than were younger women.[141][EL=1+]

Re-analyses of menstrual diaries (n=287) from one RCT[152] investigated bleeding patterns in women with post-abortal and post-menstrual insertion of Nova-T IUD (, copper surface 200, discontinued in 2001) and LNG-IUS. Nova-T IUD users had more bleeding days than LNG-IUS users. Women receiving LNG-IUS post-abortally had fewer bleeding days than women receiving it post-menstrually. The removal of the superficial endometrium during termination of pregnancy may result in these improved bleeding patterns.[157][EL=1+]

Summary of evidence

- **Amenorrhoea is more likely to occur in IUS users than copper IUD users.**

Management of bleeding problems

Heavier and longer menstrual bleeding can be treated with non-steroidal anti-inflammatory drugs (mefenamic acid) or antifibrinolytics (tranexamic acid). One RCT (n=25) reported a significant reduction in mean total blood loss during treatment with mefenamic acid when compared with placebo. [158][EL=1-] One RCT (n=19) compared tranexamic acid, diclofenac sodium and placebo in the treatment of excessive blood loss in IUD users (types not specified). It reported significant reduction by 54% in mean blood loss in IUD users treated with tranexamic acid when compared with placebo. Treatment with diclofenac sodium also reduced blood loss by 20% when compared with placebo. Neither treatment reduced pelvic discomfort during menstruation or shortened its duration.[159][EL=1+] One crossover RCT (n=20) reported significant reduction in menstrual loss in IUD users (Copper 7, copper T220, copper T380 and Lippes Loop, all unlicensed) treated with ibuprofen when compared with placebo.[160][El=1-] Another crossover RCT (n=34) reported significant reduction in menstrual bleeding in IUD (types not specified) users treated with high and low-dose naproxen when compared with placebo.[161][EL=1-]

A cohort study reported that complaints of bleeding are not associated with a misplaced device demonstrated by ultrasound scan but this should be considered in women with persistent bleeding.[162][EL=3]

WHOSPR recommends a short course of non-steroidal anti-inflammatory drugs (NSAIDs), taken during the days of bleeding, to treat spotting or light bleeding. Gynaecological pathology, pregnancy and infection should be excluded if abnormal bleeding persists.[76][EL=4]

Summary of evidence

- **Mefenamic acid, NSAID and tranexamic acid are effective in the treatment of heavy bleeding with IUD use.**

Recommendations:

Heavier bleeding with IUD use can be treated with non-steroidal anti-inflammatory drugs and tranexamic acid. [B]

Women who find heavy bleeding in association with a copper IUD unacceptable may consider changing to a LNG-IUS (Levonorgestrel intrauterine system). [D/GPP]

4.5.2 Anaemia

The increase in menstrual blood loss associated with the use of copper IUDs may have the potential to cause iron-deficiency anaemia.

One RCT compared menstrual blood loss (MBL) and haematological parameters in MLCu250 users (n=16) and MLCu375 users (n=18). It reported a significant increase in MBL from baseline in both groups at 3 months. This increase remained unchanged throughout 12 months. There was no significant difference in MBL between the two groups prior to insertion, or at 3, 6 and 12 months. There was no significant difference in haematological parameters (Hgb, haematocrit, erythrocyte count and ferritin) between the 2 groups before or after IUD use. The haemoglobin concentrations were 135 g/l and 133 g/l for MLCu250 users before and 3 years after the study. The corresponding data for the MLCu375 were 139 g/l and 137 g/l respectively. The women enrolled for this study were healthy and had regular menstrual cycles.[163][EL=1+] This RCT was continued for 3 years and no significant differences were reported between the 2 groups in MBL and haematological parameters.[164][EL=1+]

Summary of evidence

- **Menstrual blood loss is common with use of copper IUDs.**

Recommendation:

Women with established iron-deficiency anaemia should not usually use a copper IUD. [D/GPP]

4.6 Common concerns and symptoms

4.6.1 Weight change

Weight fluctuation in women of reproductive age is common, whether or not hormonal contraceptives are used. The prevalence of being overweight is increasing worldwide. It is estimated that 25% of women in the UK are categorized as obese. [165] A 7-year chart review of copper IUD users in Brazil (n=1679) reported a tendency to gain weight during the women's reproductive years, regardless of the contraceptive methods used. In this study, older women tended to gain more weight than younger women. [166][EL=3]

A European RCT reported no evidence of a difference in body weight change among women using the copper releasing Nova-T (copper surface 200)(n=937) or the hormone releasing LNG-IUS (n=1821). In this study, the mean weight at baseline was 61.6 (SD 10.6) kg in the Nova-T group and 62.0 (SD 10.0) kg in the LNG-IUS group. The mean weight had increased to 64.4 kg in both groups at 5 years (a mean increase of 2.5 kg in the Nova T group versus 2.4 kg in the LNG-IUS group). Removal of the device due to weight gain was however significantly different between LNG-IUS (1.5%) and IUD users (0%).[152][EL=1+]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a significant difference in the occurrence of weight gain (0.7% in the LNG-IUS group versus 0.4% in the IUD group), but no difference in the discontinuation rate due to weight gain or weight loss over the 7 years.[141][EL=1+]

A 5-year multicentre controlled cohort study (n=16,021), undertaken mainly in developing countries, reported significant difference in weight gain among users of Norplant, IUD (copper and non-copper) and sterilisation (4.5 versus 0.9 versus 0 per 1000 women-years respectively)(RR 6.94; 95% CI 4.57 to 10.5). For reported weight loss, the data were 1.2 versus 0.5 vs 0.1 per 1000 women-years (RR 2.64; 95% CI 1.49 to 4.67)[112][EL=2-]

Summary of evidence

- **No evidence of significant weight change in IUD users.**

Recommendation:

Women should be informed that there is no evidence that the use of the IUD affects weight. [C]

4.6.2 Altered libido and mood

The experience of sexual dysfunction, such as loss of libido, is common among young women, ranging from 5 -10% in one literature review[167] to about 30% in a national survey in the USA.[168]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no difference in the occurrence of 'frigidity' (0.4% in the LNG-IUS group versus 0.4% in the TCu380A IUD group), or depression (1.2% in the LNG-IUS group versus 1.1% in the TCu380A IUD group).[141][EL=1+].

A cohort study (n=1073) reported no differences in a decrease of sexual desire between OC and IUD (MLCu375, Nova-T, Gyne T380) users (OR 1.32, 95% CI 0.70 to 2.49). However, sexual desire decreased with age and was lower in nulliparous women and in those with an average or poor relationship with their partners.[169][EL=2-]

A 5-year multicentre controlled cohort study (n=16,021), undertaken mainly in developing countries, reported significantly fewer women with mood disorders

whilst using IUDs (copper and non-copper) compared with Norplant and sterilisation (1.2 versus 2.8 versus 2.2 per 1000 women-years). The figures for 'premenstrual tension' were 0.7 versus 1.3 versus 0.8 per 1000 women-years.[112][EL=2-]

Summary of evidence

- **There is no difference in mood/libido between users of IUD and IUS. IUD users are less likely to report mood disorders and premenstrual tension than implant users.**

Recommendation:

Women should be advised that changes in mood and libido were similar whether using IUDs or LNG-IUS, and the changes are small. [C]

4.7 Risks

4.7.1 Cardio-vascular disease

A cohort study in Thailand comparing long term DMPA users (n=50) with IUD users (n=50) (TCu380A) reported no significant difference in systolic and diastolic blood pressure between the two groups at 120 months.[170][EL=2+]

In the current WHOMEC, copper IUDs are assigned category '2' for women with valvular heart disease. WHOMEC recommends that prophylactic antibiotics be used at the time of insertion to prevent endocarditis.[16] A small study identified transient bacteraemia from vaginal organisms in 13% of women within 10 minutes of IUD replacement/insertion.[171][EL=3]

For gynaecological procedures, it is recommended that antibiotic prophylaxis is given only to women with prosthetic valves or who have had endocarditis previously. In these circumstances an intravenous regimen is advised. In the absence of specific guidance, the FFPRHC considers that such prophylaxis should be used for both insertion and removal.

4.7.2 Ectopic pregnancy

An ectopic pregnancy refers to any pregnancy that occurs outside the uterus. The absolute risk of ectopic pregnancy (ie, the risk that a woman will experience an ectopic pregnancy) is a function of the absolute risk of pregnancy in combination with the conditional risk of ectopic pregnancy (ie, the risk that a pregnancy will be ectopic). All methods of contraception decrease the risk of ectopic pregnancy as they reduce the absolute risk of pregnancy. The *relative* likelihood of a pregnancy being ectopic is greatly increased when a woman becomes pregnant during IUD use.[172] The ectopic pregnancy rate in women generally increases with age; however IUD failure rates decline with age.

Copper IUDs

Interim results from a WHO randomized comparative trial reported significantly higher ectopic pregnancy rates among women using Multiload 375 than women using TCu380A at 3 years (2.8 vs 1.4 per 100 women). After 10 years, women using TCu380A had a significant higher ectopic pregnancy rate than women using the Multiload 375. (0.8 vs 0.1 per 100 women respectively). The total number of women completing 10 years was 727. [130-132][EL=1+]

A systematic review of four RCTs [136-139] reported low ectopic pregnancies in both users of frameless IUDs and TCu380A. One of the studies reviewed [138] reported no significant difference in cumulative ectopic pregnancies, with a rate of 0.06% among users of the frameless IUD compared to 0.46% with users of TCu380A (RR 0.20; 95% CI 0.02 to 1.65)[140][EL=1++]

One RCT comparing TCu380A IUDs with TCu220 IUDs (not licensed) reported cumulative discontinuation rates due to ectopic pregnancy of 0.1 per 100 woman-years at 3 and 5 years, 0.4 per 100 woman-years among TCu380A users at 8 and 10 years.[123][EL=3]

A secondary analysis of a number of studies estimated absolute annual ectopic pregnancy rates of 0.02 per 100 TCu380A users and 0.3 to 0.5 per 100 non-contraceptors, taking into consideration the conditional risk of annual ectopic pregnancy of 6 per 100 pregnancies (6%) among TCu380A users and 1.4 among non-contraceptors (1.4%). This study reported ectopic pregnancy rates of 0.2 ± 0.1 per 1000 women years for both TCu380A and MLCu375 users at 2 years.[116;173][EL= 3]

Summary of evidence

- **The overall rate of ectopic pregnancies is low for copper IUDs.**

Copper IUDs versus other contraceptive methods

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported an ectopic pregnancy rate of 0.6 vs 0.0 per 1000 woman-years among TCu380A and LNG-IUS users respectively at 5 and 7 years. [142;143][EL=+-]

One European multi-centre RCT compared LNG-IUS (n=1821) and Nova T IUD (n=937). The ectopic pregnancy rates were 0.25 versus 0.02 per 100 woman-years in the Nova T group compared to the LNG-IUS group respectively during the 5 year period.[152][EL=1+]

Interim results from the WHO international muticentred RCT (n=3815 insertions) reported no significant difference in the discontinuation rates due to ectopic pregnancy among users of TCu380A IUD and LNG-IUS after 6 years (0.1 versus 0.0).[131][EL=1+]

A 5-year multicentre controlled cohort study (n=16,021), undertaken mainly in developing countries, reported ectopic pregnancy rates for users of copper IUDs (n=18), Norplant (n=10) and sterilisation (n=1) of 0.68 versus 0.30 versus 0.13 per 1000 women years.[174][EL=2-]

A multinational case-control study (n=1108) reported that a past history of PID

or sexually transmitted disease in current IUD users was associated with an increased risk of ectopic pregnancy compared to pregnant and non-pregnant controls. IUD use prior to conception among pregnant women did not affect the risk of ectopic pregnancy.[175][EL=2-]

Summary of evidence

- **The ectopic pregnancy rate is higher in copper IUDs than LNG-IUS but is not clinically significant.**

Recommendations:

Women should be reassured that the overall risk of ectopic pregnancy with copper IUD use is reduced compared with using no contraception. However, women who become pregnant with an IUD in place should have intrauterine and ectopic pregnancy excluded. [D/GPP]

Women should be advised that in the event of IUD failure the risk of ectopic pregnancy is less than 0.2%. [C]

4.7.3 Actinomyces-like organisms

Actinomyces israelli are commensal bacteria of the female genital tract. Actinomyces-like organisms (ALOs) are found in women with and without an IUD.[176-179] The role of actinomyces-like organisms in infection in IUD users is unclear.[180] They may be identified on cervical smears, but have not been shown to be predictive of any disease.[120;181-183]

Copper IUDs

IUDs users may have a higher risk of infection with actinomyces-like organisms compared to non-users. A non-comparative study of asymptomatic IUD users with untreated ALOs followed up for 2 years reported no occurrence of PID.[184][EL=3]

Copper IUDs versus other contraceptive methods

A Swiss study of 156 women found the incidence of actinomyces-like organisms to be significantly higher among women using Multiload Cu375 than women using LNG-IUS (20% versus 2.9% at 22 months of follow-up).[185][EL=3] However, differences between the prevalence rates however may be attributable to cervical sampling and staining techniques, population characteristics, and the potential for bias associated with retrospective reviews of case notes.

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a similarly low incidence of actinomyces on cervical smears (0% versus 0.1%) in both the LNG-IUS and the TCu380A IUD group.[141][EL=1+]

Previous recommendations suggested follow-up every 6 months for a woman choosing to continue using an IUD in the presence of ALO.[186][EL=4]

However, currently there is little research to support routine follow-up unless symptoms occur.

Recommendation:
The presence of actinomyces-like organisms on a cervical smear in a woman with a current copper IUD requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. [D/GPP]

4.7.4 Pelvic inflammatory disease (PID)

A major cause of pelvic inflammatory disease (PID) is Chlamydia trachomatis, a sexually transmitted infection of the genital tract. PID results in chronic abdominal pain, ectopic pregnancy and can lead to tubal factor infertility. [187] Chlamydia trachomatis is the most common STI in the UK and Europe, present in 11% of the sexually active population aged 19 or younger.[188][EL=3] Asymptomatic chlamydial infection can only be detected by screening. Uterine

instrumentation carried out as part of IUD insertion may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic PID. The Chief Medical Officer's Advisory Group on Chlamydia recommends consideration of opportunistic screening of any woman undergoing instrumentation of the uterus because of a resultant risk of ascending infection.[189][EL=4]

The annual incidence of PID is estimated to be 1-2% in women of reproductive age in the US.[190] A review of the WHO's IUD clinical data from 12 RCTs (n=22,908 insertions, 51,399 women-years of follow-up) reported an incidence of PID of 1.6 per 1000 woman-years, whichever type of IUD was used. PID was significantly associated with the insertion of the IUD within the first 20 days (RR 6.30, 95%CI 3.42-11.6) and with women below the age of 25 years (RR 2.45, 95% CI 1.36-3.85).[191][EL=1+]

Copper IUDs

(See 4.4 discontinuation rates)

A systematic review of 4 RCTs reported no significant difference in removal due to PID (0.1% with frameless vs 0.4% with TCu380A at 3 years (RR 0.80; 95% CI 0.23 to 2.81).[140][EL=1+]

Discontinuation due to PID was reported to be 1.2% vs 1% among users of TCu380A and MLCu375 respectively at 1 year.[126][EL=1+]

A multicentre RCT reported the rate of PID among TCu380A and MLCu375 users at 3 years (7.0 vs 4.6).[127;128][EL=1+]

Another RCT reported no significant difference in PID rates of 1.3 vs 0.6 among TCu380A and MLCu375 users at 2 years.[129][EL=1+]

A non-comparative study (n=574) in the UK reported a cumulative discontinuation rate of 0.9 due to PID at 5 years among Nova-T 380 users.[134][EL=3]

Copper IUDs versus other contraceptive methods

(See 4.4 discontinuation rates)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu380A users in discontinuation rate due to PID (0.9% versus 0.8%, 1.4% versus 1.2%, and 1.6% versus 1.5% at 1-2 ,3-5 and 6-7 years respectively).[141-145][EL=1+]

One European multicentre RCT, which compared IUS-20 (n=1821) and Nova T IUD (n=937) (copper surface 200), reported cumulative rates for removal due to PID of 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5%, and 0.6% versus 1.6% at 1, 2, 3, 4 and 5 years respectively.[151-154][EL=1+]

Interim results from the WHO international muticentred RCT (n=3815 insertions) showed no significant difference in discontinuation rates due to PID between LNG-IUS users and TCu380A IUD users at 6 years (0.3 versus 0.1).[131;132][EL=1+]

A 5-year multicentre controlled cohort study (n=16,021), undertaken mainly in developing countries, reported the occurrence of acute PID in IUD (copper and non-copper) users (n=18) compared to Norplant (n=6) and sterilisation (n=2) (0.6 versus 0.2 versus 0.3 per 1000 women years).[174][EL=2-]

For IUD users who have been diagnosed with PID, testing for relevant organisms and appropriate antibiotics should be initiated. The UKSPR recommends that removing the IUD provides no additional benefit once PID is being treated with appropriate antibiotics.[78][EL=1-4]

Prevention of PID

A meta-analysis of 4 RCTs reported little benefit with prophylactic antibiotic

use to cover IUD insertion among women at low risk for STI. Women at low risk of STIs who use IUDs have a low risk of PID. Overall, the odds ratios for pelvic inflammatory disease associated with use of prophylactic doxycycline 200mg or azithromycin 500mg compared with placebo or no treatment was 0.89 (95%CI 0.53-1.51). Use of prophylaxis was associated with a small reduction in unscheduled visits to the provider (OR 0.82; 95% CI 0.70-0.98). Use of doxycycline or azithromycin had little effect on the likelihood of removal of the IUD within 90 days of insertion (OR 1.05; 95% CI 0.68-1.63).[192][EL=1++] In 2 RCTs included in this review, users of the TCu380A showed no significant difference in the occurrence of PID with or without prophylactic antibiotic use, with respective odds ratios of 1.0 (95% CI 0.06 to 15.95)[193] and 0.98 (95%CI 0.06 to 15.73).[194][EL=1+]

Recommendations:

Women should be informed that the chance of developing pelvic inflammatory disease following a copper IUD insertion is very low in women at low risk of sexually transmitted infection, at less than 1% over 1 year. [C]

All women should be offered screening for infections STIs before IUD insertion and women at risk of STIs should be strongly encouraged to accept the offer. [D/GPP]

Where screening is not possible, or where screening has not been completed, use of prophylactic antibiotics is recommended in women with increased risk of STIs. [D/GPP]

4.7.5 Uterine perforation

Perforation of the uterus is a serious but uncommon complication of IUD insertion.

Copper IUDs

One RCT undertaken in Nigeria (n=200) reported no perforation among Multiload Cu375 users (n=100) compared to one perforation among CuT380A users (n=100) at 1 year.[126][EL=1+]

A multicentre RCT reported no perforation among women using Multiload Cu375 (n=740) or TCu380A (n=737) at 3 years.[127;128][EL=1+]

Interim results from a WHO randomized comparative trial reported no perforation among women using Multiload 375 compared to women using TCu380A at 3 years. No data on perforation were available at 10 years.[130-132][EL=1+]

A systematic review of 4 RCTs evaluated the effectiveness of frameless IUDs and TCu380A IUDs. It reported one perforation with Gynefix and none with TCu380A IUDs.[140][EL=1++] No perforations were reported in an audit of 138 insertion of Gynefix IUDs. The authors commented on the importance of the skills and dexterity of the clinician during insertion of the frameless device which needs to be implanted with precision into the myometrium. The anchoring technology of the frameless IUD requires skills and competence to avoid complications. [195][EL=3]

Another non-comparative study (n=8343) in Turkey reported an incidence of 2.2 perforation per 1000 insertions of TCu380A IUD at 1 year. The risk of perforation may be associated with insertion 0-3 months postpartum.[196][EI=3]

A non-comparative study (n=574) in the UK reported no perforations after insertion of Nova T380 at 5 years.[134][EL=3]

A non-comparative study (n=17469) from New Zealand reported an incidence of perforation of 1.6 per 1000 MLCu375 insertions over 6 years. Of the 28 perforation events reported, 27 were related to IUD insertion and one was related to the introduction of the uterine sound prior to insertion of the device. This reported incidence is almost certainly an underestimate, as many perforations probably go unrecognized and events not requiring hospital treatment may not have been reported.[197][EL=3] Another study, using an international dataset of over 21500 insertions. estimated the perforation rate to be 1.5 per 1000 insertions among TCu380A users and 2.3 per 1000 insertions among MLCu375 users.[198][EL=3]

Copper IUDs versus LNG-IUS

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a similarly low discontinuation rate due to uterine perforation (0.1% versus 0%) and cervical perforation (0% versus <0.1%) between the LNG-IUS users and TCu380A users at 7 years.[141][EL=1+]

The FFPRHC endorses a 6-week interval after an asymptomatic, suspected perforation before IUD insertion is attempted again.[199][EL=4]

Summary of evidence

- **Uterine perforation associated with IUD and LNG-IUS use is low : less than 1%.**

Recommendation:

Women should be reassured that the risk of uterine perforation at the time of IUD insertion is very low (less than 1 in 100). [C]

Women should be advised on symptoms of uterine perforation, which would warrant an early review. [D/GPP]

Women should be informed that the risk of perforation is related to the skill of the healthcare professional inserting the device. [D/GPP]

4.7.6 Women who become pregnant while using an IUD

Approximately 6% of pregnancies occurring in women using an IUD are ectopic.[116] IUDs should not be used during pregnancy and they are assigned category '4' by WHOMEC.[16]

Spontaneous miscarriage is the most frequent complication of pregnancy with an IUD in place. About 50% to 60% of uterine pregnancies spontaneously abort if the IUD is not removed, against a background rate of 13%.[200][EL=3]

If pregnancy occurs with an IUD in situ, removal of the IUD to avoid the risk of miscarriage, pre-term delivery and infection is recommended by the UKSPR. [78][EL=4] The IUD may be removed at the time of a therapeutic termination of the pregnancy, if that was the woman's intention.

Recommendations:
Women who become pregnant with the IUD in situ should be advised to consult early to exclude ectopic pregnancy. [D/GPP]

If the pregnancy is before 12 weeks and the IUD can be easily removed, it should be removed regardless of the woman's intentions to continue or terminate the pregnancy. [D/GPP]

4.8 Return to fertility

Copper IUDs

Data for nulliparous women from a cohort study (n=1071) suggested that long-term IUD use was associated with reduced fertility.[201] These findings could be explained by bias (IUD users differed from non-IUD users in that they were older, had higher rates of previous miscarriage, termination and ectopic

pregnancy) or confounding factors (STIs may have accounted for these findings rather than the IUD itself).[202] It was suggested that re-insertion of IUDs which were licensed for use for no more than 2 or 3 years, could lead to increase in PID, leading to reduced fertility. [203][EL=3]

A cohort study in New Zealand assessed fertility rates and pregnancy outcomes after removal of a variety of copper intrauterine contraceptive devices in nulligravid women (n=375) and gravid women (n=676). Within 48 months, 91.5% of the nulligravid and 95.7% of the gravid women had conceived. A 2-year combined study, with regard to longer use of intrauterine contraceptive devices (greater than 2 years), showed no significant reduction in fertility and no increase in ectopic pregnancy within 24 months.[204][EL=2+]

A case-control study found that previous copper IUD (types not specified) use in nulliparous women did not increase the risk of tubal occlusion and infertility when compared with infertile controls (OR 1.0, 95% CI 0.6 to 1.7).[205][EL=3]

Copper IUDs versus LNG-IUS

A multinational European RCT compared the recovery of fertility between ex-users of LNG-IUS (n=139) and Nova T (n=71) (copper surface 200,). There was no significant difference in cumulative conception rates between ex-LNG-IUS users and ex-Nova-T users (79.1% versus 71.2%) at 1 year (86.6% versus 79.7%) or at 2 years. Ninety-six percent of the pregnancies occurred during the first year after removal and 84% of the pregnancies in the Nova-T group and 86% in the LNG-IUS group ended in live births.[154][EL=1+]

Another RCT reported a pregnancy rate of 96.4% in ex-LNG-IUS users (n=60) compared to 91.1% in ex- TCu380A IUD users (n=50) at 1 year.[146;206][EL=1+]

A questionnaire survey of pregnant women in the UK reported mean time to pregnancy (TTP) of 2.0, 2.2 and 3.9 times longer after discontinuation of COC (n=925), IUD (n=82) and injectable (n=62) respectively when compared with condom use (n=389). Conception rates within 6 months of discontinuation

were 71%,77%, 27% and 25% among users of COC, IUDs, injectable and implants (n=4) respectively, compared to 82% among condom users. Relative to condoms, the odds of subfecundity were 1.9, 5.5 and 2.9 respectively among users of COC, injectable and short-term IUD.[207][EL=3]

Recommendation:

Women should be informed that there is no evidence for any delay in return of fertility following removal or expulsion of the copper IUD. [C]

4.9 Details of method use

4.9.1 Assessment prior to fitting

(See 3.6)

The WHOSPR and UKSPR recommend that physical examination, including pelvic/genital examination, medical history and STI risk assessment are essential and mandatory before providing IUDs as a method of contraception. Breast examination, cervical screening, routine laboratory tests, haemoglobin test and blood pressure screening are not recommended.[76;78][EL=4] Women with identified risk of STI should have their decision on their chosen method of contraception reviewed and alternative methods should be discussed.

Recommendations:

Health professionals fitting a copper IUD should have reasonably excluded relevant genital tract infection (cervical or pelvic) (chlamydia, gonorrhoea and pelvic inflammatory disease) by assessing sexual history, clinical examination and undertaking laboratory tests. [D/GPP]

Women with identified risks associated with uterine or systemic infection should have investigation, appropriate prophylaxis or treatment instigated prior to insertion of a copper IUD. [D/GPP]

4.9.2 Information prior to insertion

See 3.5

Recommendations:

Women should be advised of failure rates, benefits, risks and side effects of the copper IUD. [D/GPP]

Women should be informed that insertion of an IUD may cause pain and discomfort for a few hours and light bleeding for a few days following insertion and should be advised about appropriate pain relief. [D/GPP]

4.9.3 Position of IUD within the uterine cavity

We found no evidence that assessed the effect of the position of IUD within the uterine cavity.

Recommendation:

Women should be informed that the effect of the position of an IUD within the uterine cavity, in relation to contraceptive efficacy, is not known. [D/GPP]

4.9.4 Time of fitting of IUD

In a normal menstrual cycle

Having reasonably excluded pregnancy, an IUD may be inserted at any time during the menstrual cycle.[16] An IUD can be inserted up to 5 days after the first unprotected sexual intercourse in a cycle, or up to 5 days after the earliest date of ovulation.

When switching methods

The UKSPR and the FFPRHC both recommend that the copper IUDs can be inserted immediately if it is reasonable certain that the woman is not pregnant. [78;199][EL=1-4]

Following termination of pregnancy

Insertion of an IUD immediately following induced abortion has advantages in that the woman is known not to be pregnant, her motivation for effective contraception is likely to be high, and she is presently in a health care setting.

A systematic review of 9 RCTs (mostly comparing IUDs not currently used in the UK) reported that insertion of IUD immediately after abortion is both safe and practical. IUD expulsion rates appeared higher than after interval insertions.[208][EI=1++] One of the RCTs from this review compared LNG-IUS with Nova-T IUD inserted at the time of elective termination of pregnancy. It reported significantly lower cumulative pregnancy rates (0.8 vs 9.5 per 100 women) but significantly higher cumulative discontinuation rates in LNG-IUS users due to hormonal reasons (15.9 vs 3.9 per 100 women) at 5 years. [209][EI=1+]

Case-control studies reported that the risk of uterine perforation following IUD insertion within 30 days of a TOP is low. The controls were medical and surgical controls. [210][EL=3] Only three perforations were identified in 2348 such insertions in a WHO study.[211][EL=2-] Re-admission rates for pelvic infection were not increased by IUD insertion immediately following a first-trimester TOP.[212][EL=3]

There are few data specifically relating to IUD insertion following medical TOP. The FFPRHC recommends that an IUD may be inserted immediately (i.e. within 48 hours) following first- or second-trimester medical TOP. Otherwise, insertion should be delayed until 4 weeks following medical TOP (as for postpartum insertions).[199][EL=3]

In the current WHOMEC, copper IUDs are assigned category '2' for insertion in women after second trimester abortion and category '4' for insertion in women immediate after post-septic abortion.[16]

The RCOG abortion guideline recommended that IUD can be inserted immediately following a first- or second-trimester termination of pregnancy. [213][EL=1- 4]

Post delivery

A systematic review of 8 RCTs (mostly comparing IUDs not currently used in the UK) reported that post-partum insertion of IUDs appeared safe and effective.[214][EL=1++] One cohort study compared insertions of the progestogen vaginal ring (n=802) and TCu380A (n=734) during lactation in postpartum women (mean time of postpartum insertion 47.6 days after delivery) and reported no significant difference in pregnancy rate (1.5% vs 0.5%) and a significant difference in expulsion rate (8.1% vs 5.6%) between the two groups at 12 months. [215][EL=2-]

Established practice in the UK has been to delay insertion until 6–8 weeks postpartum. WHOMEC, however, recommends that the benefits of IUD use 4 or more weeks after delivery outweigh any risks.[16] This unrestricted use includes women who are breastfeeding, not breastfeeding or who have been delivered by Caesarean section. WHOMEC suggests an increased risk of uterine perforation if an IUD is inserted between 48 hours and 4 weeks postpartum and therefore the risks of insertion during this time generally outweigh the benefits. A review of studies provided 2-year follow-up data on 6,816 woman-months of experience following IUD insertion between 4 and 8 weeks postpartum and 19,733 woman-months of experience following IUD insertion more than 8 weeks postpartum. No perforations were identified and discontinuation rates were similar in the two groups, suggesting an IUD can be inserted safely after 4 weeks postpartum.[216][EL=3] WHOMEC suggests an increased risk of expulsion if an IUD is inserted within the first 48 hours

postpartum, but the benefits of immediate IUD insertion generally outweigh the risks. A non-comparative study included 734 breastfeeding women with a mean time of insertion of a TCu380A of 47.6 days postpartum (SD 9.9). It showed an expulsion rate at 12 months of 5.6 per 100 insertions.[215][EL=2+] Women with current puerperal sepsis should be advised against insertion of an IUD.[217][EL=4]

Recommendations:

Copper IUDs can be inserted at any time during a menstrual cycle. [D/GPP]

Copper IUDs can be inserted immediately or at any time following first and second trimester termination of pregnancy. [D/GPP]

Copper IUDs can be inserted from 4 weeks post partum irrespective of the mode of delivery if it is reasonably certain that the woman is not pregnant. [D/GPP]

4.10 Training of health professionals

(See 3.14)

A large prospective study, which included 17,469 Multiload Cu375 insertions by 1,699 doctors, reported an incidence of 1.6 uterine perforation per 1000 insertions at 6 years. Doctors who reported performing fewer than 10 IUDs insertions in the 6-year period reported significantly more perforations than doctors who performed between 10 to 49 IUD insertions (RR 2.3; 9%% CI 0.99 to 5.26) and doctors who performed between 50 to 99 IUD insertions (RR 7.3; 95%CI 0.94 to 56.3) in the same study period.[197][EL=2+]

A secondary analysis of TCu380A acceptors from one RCT in three developing countries compared insertion failures and complications between non-physician (n=174) and physician insertions (n=193). It reported an overall significantly higher cumulative discontinuation rate due to expulsion (8.6% vs 2.7%), and bleeding/pain (8.1% vs 1.4%). Over all continuation rate was lower

(77.3% vs 85.5%) at 12 months. This suggested that appropriate competency-based training is required to limit the number of expulsions and removals for bleeding and pain by non-physicians.[218][EL=2+]

A cohort study compared IUD insertions by specialist nurses (n=22) and doctors (n=28). It reported that adequately trained nurses were proficient and safe at IUD insertions, regardless of the woman's parity.[219][EL=2-]

It has been suggested that the performance of IUDs in comparative trials are often reflective of operator skills and quality of care and follow-up, rather than the nature of the device studied. [140][EL=1++][220][EL=4] IUD expulsion rates were reported to be significantly higher for inexperienced inserters. [221][EL=1+]

The FFPRHC has specific training requirements for health professionals wishing to obtain a letter of competence (LoC) in intrauterine techniques (IUT). Competence in gynaecological examination and the assessment, management and investigation of women with IUD problems are required for all health professionals inserting IUDs. Recertification should ensure continuing competence. The letter of competence (LoC) must be updated every five years, with at least 2 hours of relevant continuing education and a log of at least 12 insertions in 12 months or six in 6 months using at least two different types of device in unanaesthetised patients.

The Royal College of Nursing Sexual Health Forum has issued training guidance and requirements for nurses wishing to insert IUDs.[105][EL=4] It outlines eligibility criteria for adequate training (for example, obtain a recognised family planning/contraception qualification), and the knowledge and skills required to perform insertion and explain various aspects of care. Nurses can receive training from experienced doctors with a letter of competence in intrauterine techniques (LoC IUT). Nurses must also observe a minimum of five insertions, and fit a minimum of ten devices of varying types.

Recommendation:

IUDs should only be fitted by trained personnel with continuing

experience of fitting at least one copper IUD or one LNG-IUS a month. [D/GPP]

4.11 Specific groups

Adolescents

We did not identify any studies which assessed the use of copper IUDs in adolescents.

Copper IUDs are assigned category '2' for women aged from menarche to under 20 years.[16]

Nulliparity

The majority of RCTs conducted have examined the use of IUDs among parous women worldwide. There is concern that nulliparity is related to an increased risk of expulsion among IUD users. In the current WHOMEC, the copper IUDs are assigned category '2' for nulliparous women and '1' for parous women. [16][EL=3]

Women over 40 years of age

An observational study followed 50 women inserted with a CuT380A at age 40 or older and who used the device at least 36 months.[222][EL= 3] No pregnancies, cases of PID or expulsions occurred during the study period. Inter-menstrual bleeding was the commonest reported side effect (n=15, 95%CI 17.9 to 44.6) followed by pain and dysmenorrhea. Similar results were reported in a smaller study of first time IUD users over 40 years of age with 6 months of follow-up.[223][EL=3]

A RCT of women requesting an IUD who received either a Multiload Cu250 (n=2856) or a Multiload Cu375 (n=3606) analysed the safety of IUD use in

different age groups.[224][EL=3] Pregnancy rates were lower in older women. Expulsion and bleeding and/or pain rates were higher for younger women receiving both IUD types ($p<0.01$).

Refer to recommendation at 4.1.2.

Recommendations:

IUDs may be inserted in adolescents. However, STI risk and Fraser competence should be considered. [D/GPP]

Women should be informed that nulliparity at any age is not a contraindication to IUD insertion. [D/GPP]

Women should be informed that women of all ages can use copper IUDs. [D/GPP]

Women with body mass index (BMI) over 30

We did not identify any studies which addressed this question.

In the current WHOMEC, copper IUDs are assigned category '1' for women over 30 kg/m^2 body mass index.[16]

Women who are breastfeeding

A cohort study reported no increase in copper levels in breast milk in breastfeeding mothers with an IUD (TCu380A and Cu200B) (n=62) inserted at 10-weeks post-partum, when compared with a third group that were not using an IUD (n=33).[225][EL=2-] Another cohort study reported no change in the amount and composition of breast milk between POC users (n=42) and copper IUD users (n=41) at 4 months follow-up.[226][EL=2-]

Recommendation:
Women should be informed that copper IUDs can safely be used by women who are breastfeeding. [C]

4.12 Medical conditions and contraindications

Diabetes

A literature review which evaluated contraceptive methods for women with type 1 diabetes, type 2 diabetes and those with a history of previous gestational diabetes reported no increase in PID in these women in association with copper IUDs.[227][EL=4]

A non-comparative study reported that the TCu380A is a safe and effective device for women with type 2 diabetes. Women requesting a TCu380A (n=176) were followed for 5 years at a family planning clinic in California. Participants were more likely to be obese and to have already given birth. Continuation rates were high (93% and 70%) at 1 and 3 years respectively. The pregnancy rate was 1.57% per 100 woman years and expulsion rate 1.96%.[228][EL=3]

These rates are comparable with those found in randomised studies of parous women.[229][EL=2+]

In the current WHOMEC, copper IUDs are assigned category '1' for women with diabetes.[16][EL=4]

Recommendation:
Women should be informed that diabetes poses no restriction to use of copper IUDs. [D/GPP]

Epilepsy

We did not identify any studies.

In the current WHOMEC, Copper IUDs are assigned category '1' for women with epilepsy and who are on anti-epileptic drugs.[16][EL=4]

Recommendation:
Emergency drugs including anti-epileptic medication should be available at the time of fitting a copper IUD in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation. [D/GPP]

Sexually transmitted infections, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)
(See 3.11)

Theoretical concerns exist about the increased risks of complications, such as PID in IUD users with HIV/AIDS and risks of transmission to sexual partners.

A systematic review of three studies to update the WHOMEC found limited data and reported no evidence of risks of pelvic infection and of transmission to partners from IUD users with HIV/AIDS. In HIV-infected and non-infected women after IUD insertion, there was no difference between the overall complications and infection-related complications at 2 years follow-up (hazard ratio 0.98, 95% CI 0.59 to 1.60, result of one cohort study). There was no significant difference in the incidence of PID, which was low in both groups (2% in HIV-infected women versus 0.4% in non-infected women). For women at risk of HIV, IUDs were associated with a non-significant decrease in seroconversion (RR 0.8, 95% CI 0.38 to 1.69, result of one study). As women at risk for HIV will also be at risk for other STIs, these women will be at increased risk of adverse outcomes such as PID if they use IUD. There are no studies available of women at high risk of HIV.[230-233][EL=2-]

In the current WHOMEC recommendations, IUD is assigned category '2' for initiation and continuation for women who are at high risk of HIV and who are HIV-infected. For women with AIDS, IUD is assigned category '3' for

initiation and category '2' for continuation. For women who are clinically well on anti-retroviral therapy, IUD is assigned category '2' for both initiation and continuation.[16]

Recommendation:
The IUD is a safe and effective method of contraception for women who are HIV positive or have AIDS. Safer sex using condoms should also be encouraged. [D/GPP]

4.13 Drug interactions

Antibiotics

We did not identify any studies.

In the current WHOMEC, copper IUDs are assigned category '1' for women who are prescribed antibiotics.[16][EL=1-4]

4.14 Follow-up

The UKSPR recommends a follow-up visit after the first menses, or three to six weeks after insertion, to exclude infection, perforation or expulsion.[78][EL=4] No routine regular follow-up is required.

Recommendation:
A follow-up visit should be carried out after the first menses, or 3 to 6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be advised to return at any time to discuss problems, if she wants to change her method, or when it is time to have the IUD removed. [D/GPP]

4.15 Economic evidence

The economic analysis undertaken for this guideline evaluated the relative cost-effectiveness of IUD in comparison to the male condom, the combined oral contraceptive (COC), non-reversible contraceptive methods (male and female sterilisation) as well as the other LARC methods (injectable, IUS, implant).

Compared to male condom and COC, IUD is the dominant option (i.e. is both more effective and less costly than male condom and COC) across all time periods of contraceptive use examined, that is for one and up to 15 years.

Regarding non-reversible contraceptive methods, IUD is less effective but also less costly for up to 4 years of contraceptive use compared to male sterilisation, and 6 years of use compared to female sterilisation. Male and female sterilisation become dominant options relative to IUD for durations of contraceptive use starting from 5 and 7 years respectively, and above.

Among LARC methods IUD is the cheapest option across all time horizons examined, with the exception of the injectable, which is the least costly method when one year of contraceptive use is considered. For one year of use IUD is more effective than the injectable, with an Incremental Cost-Effectiveness Ratio (ICER) of £339 per pregnancy averted. After one year of use and up to 15 years (the maximum time frame examined), IUD dominates the injectable (i.e. both more effective and less costly).

Compared to IUS, IUD is also the dominant option between 2 and 4 years of use; after this time, it is less costly but also less effective than IUS. The ICER of IUS compared to IUD generally tends to decrease overtime, starting from £18,845 per pregnancy averted for 5 years of use, and falling at £1,884 per pregnancy averted at 15 years of use. For one year of use, the IUS is also more effective and more costly than the IUD, with an ICER of £60,322 per pregnancy averted.

IUD is constantly less effective than the implant for all periods of contraceptive use up to 15 years. For short periods of use, up to 4 years, the

ICER of the implant versus IUD ranges from £21,526 (one year of use) to £42,252 (3 years of use) per pregnancy averted. This ratio falls at £10,312 per pregnancy averted at 5 years of use, and decreases thereafter, reaching a cost of £1,617 per pregnancy averted at 15 years of use, with only slight increases at 10 and 13 years of use.

Cost-effectiveness of IUD relative to IUS and the implant is highly sensitive to discontinuation rates associated with LARC use.

Evidence statement

- **IUD is more cost-effective than the male condom and COC, even for short periods of contraceptive use (i.e. one year).**

- **Male and female sterilisation are more cost-effective than IUD for longer durations of contraceptive use, starting at 5 and 7 years respectively.**

- **IUD is more cost-effective than the injectable for 2 and up to 15 years of contraceptive use. It is also more cost-effective than IUS for periods of use between 2 and 4 years. Compared to the implant, it is both less effective and less costly. Nevertheless, its relative cost-effectiveness compared to IUS and the implant is highly affected by discontinuation rates following LARC use.**

Full results of the economic analysis are presented in chapter 8.

5. Progestogen-only intrauterine system (POIUS)

5.1 Introduction

5.1.1 What it is

The levonorgestrel intrauterine system (LNG-IUS) is a small T-shaped contraceptive device which after insertion releases 20 ug of levonorgestrel per day into the uterus. It consists of a polyethylene T-shaped frame, with a steroid reservoir around the 32 mm long vertical stem. The LNG-IUS is licensed for use of 5 years. LNG-IUS is inserted into the uterine cavity. Correct placement of the device is necessary to deliver the steroid over the whole endometrial tissue. The LNG-IUS have some similar features to the copper IUD. The LNG-IUS mediates its contraceptive action via the hormone whereas the copper IUDs contains no hormone. It may occasionally require local anaesthesia and dilatation of the cervical canal to aid insertion in nulliparous or perimenopausal women.

5.1.2 Mechanism of action

The contraceptive effects of the LNG-IUS are mediated via its progestogenic effect on the endometrium.[117] High intrauterine levels of LNG lead to functional and histological changes within the endometrium, preventing implantation.[234-236] Sperm penetration is decreased due to changes in cervical mucus.[237] Most women (>75%) will continue to ovulate.[238] [EL=3]

Recommendation:
Women should be advised that LNG-IUS as a contraceptive may act predominantly to prevent implantation and may not always prevent fertilisation. [D/GPP]

5.1.3 Use in the UK

In 2003/4, it is estimated that 1% of women aged 16-49 years in Great Britain chose LNG-IUS as their method of contraception.[1][EL=3]

5.1.4 Duration of action

The 52mg LNG is homogeneously dispersed, and the rate-limiting membrane allows LNG to be released into the uterine cavity at a constant dose of 20 µg per day for five years. However, the contraceptive effectiveness of LNG-IUS may continue for longer than 5 years.

A multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a cumulative pregnancy rate of 1.1 and 1.4 per 100 women in LNG-IUS (two different dosages used, 60mg or 46mg levonorgestrel) and TCu380A users respectively at 4 years. No pregnancies were reported among users of either device at 5, 6 and 7 years (174 LNG-IUS users, 216 TCu380A users completing the trial).[141][EL=1+]

LNG-IUS users (two different dosages used, 43mg and 56mg levonorgestrel) from one RCT[150] were followed up in a non-comparative study in Brazil (n=293) which reported no pregnancies in LNG-IUS users up to seven years of use.[239][EL=3]

LNG-IUS (containing 46mg levonorgestrel) users from another RCT[152] were followed up in a non-comparative European study (n=109) reporting no pregnancies in LNG-IUS users in seven years of continuous use. Eighty-two of these women had a new LNG-IUS inserted at 7 years. In this study LNG-IUS was reported to be safe and effective for up to 12 years, with device replacement every 5 years. At the end of the 12-year follow-up the mean age of women was 44.7years (range 33.5 to 51.5). LNG-IUS may provide an effective method of contraception, allowing a convenient and bleeding-free transition for women in their late reproductive years.[240][EL=3]

Recommendations:

LNG-IUS is licensed 5 years. [C]

Women who are aged 45 and older at the time of LNG-IUS insertion and who are amenorrhoeic can retain the device until they no longer require contraception. It is important that this is discussed with women at the time of fitting as it is outside the product licence. [D/GPP]

5.1.5 The evidence

Comparative and non-comparative studies which evaluated the effectiveness of LNG-IUS were included based on their comparability to the population of UK and of the developed countries. Trials of effectiveness in populations of women with a lower body weight than that of the UK female population may underestimate the failure rates and side effects profile. Discontinuation rates from countries where access to contraception is limited and/or expensive may differ from those in the UK. (See section 3.4 and 3.10) This criterion was also applied to one HTA report [125] (n=19 RCTs and 11 cohort studies) which assessed the effectiveness of LNG-IUS-20 (Mirena®) versus other forms of reversible contraceptives. We examined the studies reviewed and included those which met the selection criteria determined by the Guideline Development Group to be appropriate to the population of UK and the developed countries in terms of body weight and access to contraceptive service provision. (See section 3.4)

5.2 Effectiveness

LNG-IUS versus copper IUDs

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a cumulative pregnancy rate of 1.1 and 1.4 per 100 women among

LNG-IUS and TCu380A users respectively at 7 years.[141][EL=1+] Results of this RCT were documented in four other reports during the 7 years study period.[142-146]

Interim results from the WHO international muticentred RCT (n=3815 insertions) reported a significantly higher cumulative pregnancy rate among users of TCu380A IUD when compared with LNG-IUS users at 6 years (2.0 versus 0.5).[131;132][EL=1+]

One RCT compared LNG-IUS (n=141) and Nova T IUD (n=136) (copper surface 200) in Finland and Brazil and reported a pregnancy rate of 0.08/458 women years and 0.6/431 women years respectively at 5 years.[147][EL=1+] Results of this RCT were documented in 3 other reports during the 5-year study period.[148-150]

One European multicentre RCT compared LNG-IUS (n=1821) and Nova T IUD (n=937) (copper surface 200). It reported a significant difference in cumulative pregnancy rate of 0.3% versus 3.7% and 0.5% versus 5.9% in users of IUS-20 and NovaT IUD respectively at 3 and 5 years.[151;152][EL=1+] Results of this RCT were documented in two other reports during the 5-year study period.[153;154]

A non-comparative study (n=678) from the UK reported a gross cumulative pregnancy rate of 0.6 (95% CI 0.1 to 1.6), 1.0 (95% CI 0.3 to 2.4), 1.0 (95% CI 0.3 to 2.4), 1.0 (95% CI 0.3 to 2.4) and 1.0 (95% CI 0.3 to 2.4) at 1, 2, 3, 4 and 5 years among LNG-IUS users.[241][EL=3]

Summary of evidence

Table 5.1 LNG-IUS vs copper IUDs: pregnancy rates %

	Pregnancy rates %				
Studies	**TCu380A (licensed 8 years**	**Nova-T 200 (no longer licensed)**	**LNG-IUS (licensed 5 years)**	**Rate measured at point (year)**	**EL**
153 154		3.7	0.3	3	1+
		5.9	0.5	5	1+
148 149 150		<0.5	< 0.5	5	1+
131 132	2.0		0.5	6-7	1+
142 143 144	1.4		1.1	7	1+
241			0.6	1	3
			1.0	3	
			1.0	5	

- **Although there is some evidence to suggest that the IUS may be more effective than a copper IUD containing 380mm^2 copper, the difference is very small and of doubtful clinical significance.**
- **Pregnancy rates with the LNG-IUS in situ have been reported to be up to 1.0 at 5 years, and 1.1 at 7 years.**
- **The licensed duration of action of LNG-IUS is 5 years but the evidence suggests that it is effective as a contraceptive for 7 years.**
- **Repeated use of LNG-IUS is safe.**

Recommendation:

Women should be informed that the pregnancy rate associated with the use of LNG-IUS is less than 1 in 100 women over a 5-year period. [C]

5.3 Expulsion

Expulsion of an IUD occurs in approximately 1 in 20 women, and is most common in the first three months after insertion. Expulsion commonly occurs

during menstruation.[118][EL=4]

IUS versus copper IUDs

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu380A users in discontinuation rate due to expulsion (6.0% versus 5.5%, 7.3% versus 6.1%, 11.8% versus 7.4% and 11.8% versus 8.4% at 1, 2 , 5 and 7 years respectively).[141-145][EL=1+]

Interim results from the WHO international multicentred RCT (n=3815 insertions) reported no significant difference between LNG-IUS users and TCu380A IUD users in discontinuation rates due to expulsion (7.5% versus 8.2%) after 6 years.[131;132][EL=1+]

An RCT compared LNG-IUS (n=141) and Nova T IUD (n=136)(copper surface 200) in Finland and Brazil. It reported cumulative discontinuation rates due to expulsion of 0.6% versus 4.5%, 0.6% versus 6.1% and 2% versus 6% at 1, 2 and 5 years respectively).[147-150][EL=1+]

One European multicentre RCT which compared LNG-IUS (n=1821) and Nova T IUD (n=937) (copper surface 200) reported cumulative rates for removal due to expulsion of 3.4% versus 3.4%, 4.2% versus 4.1%, 4.8% versus 4.8%, 4.9% versus 5.3% and 4.9% versus 5.5% at 1, 2, 3, 4, and 5 years respectively.[151-154][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rates due to expulsion of IUS of 4.5%, 5.2%, 5.5%, 5.5% and 5.9% at 1,2, 3, 4 and 5 years.[241][EL=3]

Summary of evidence

Table 5.2 LNG-IUS vs copper IUDs: expulsion rates %

	Expulsion rates %				
Studies	**TCu380A (licensed 8 years**	**Nova-T 200 (no longer licensed)**	**LNG-IUS (licensed 5 years)**	**Rate measured at point (year)**	**EL**
[153] [154]		3.4	3.4	1	1+
		4.8	4.8	3	1+
		5.5	4.9	5	1+
[148] [149] [150]		6.0	2.0	5	1+
[131] [132]	8.2		7.5	6-7	1+
[142] [143] [144]	5.5		6.0	1	1+
	6.1		7.3	2	
	7.4		11.8	5	
	8.4		11.8	7	
[241]			4.5	1	3
			5.5	3	
			5.9	5	

- **The expulsion rates between LNG-IUS and TCu380A varied, from 7.5% vs 8.2% after 6 years. One study reported an expulsion rate of 11.8% vs 8.4% at 7 years.**

Recommendations:

Women should be advised that a LNG-IUS may be expelled but this occurs in fewer than 1 in 10 women over a 5-year period. [C]

Women should be instructed how to check for the presence of the LNG-IUS threads, and advised to do this regularly with the aim of recognising expulsion. [D/GPP]

5.4 Discontinuation and reasons for discontinuation

(See 3.10)

LNG-IUS versus copper IUDs

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA)

reported a significantly difference in cumulative discontinuation rate between LNG-IUS users and TCu380A users (24% versus 18%, 40% versus 31%, 51% versus 41%, 59% versus 52%, 67% versus 60% and 77% versus 72% at 1, 2, 3, 4, 5, and 7 years respectively). There were significant differences in cumulative discontinuation rates due to amenorrhoea (4.9% versus 0.1%, 8.4% versus 0.2%, 19.7% versus 0.4% and 24.6% versus 1.1% at 1, 2, 5 and 7 years respectively). The annual discontinuation rate due to amenorrhoea ranged from 2.5% to 6.6 % in the first 5 years. The cumulative discontinuation rates due to other menstrual problems and pain were not significantly different at 1 and 2 years (6.0% versus 7% and 8.6% versus 11.3% respectively), but were significantly different at 5 and 7 years (15.4% versus 23% and 20.4% versus 30% respectively). There were no significant differences between the 2 groups in discontinuation rate due to PID (0.9% versus 0.8% ,1.4% versus 1.2%, and 1.6% versus 1.5% at 1, 2 and 7 years respectively).[141-145][EL=1+]

Interim results from the WHO international multicentred RCT (n=3815 insertions) reported a significant difference in discontinuation rates due to bleeding problems between LNG-IUS users (n=464) and TCu380A IUD users (n=580) at 6 years (36% versus 11%). There were significant differences in discontinuation rates due to amenorrhoea (23.5% versus 0.5%), reduced bleeding (10.9 versus 3.1) and increased bleeding (5.4% versus 7.2%) in the two groups at 6 years. There was no significant difference in discontinuation rates due to PID (0.3% versus 0.1%) at and after 6 years.[131;132][EL=1+]

An RCT which compared IUS-20 (n=141) and Nova T IUD (n=136)(copper surface 200) in Finland and Brazil reported cumulative discontinuation rates of 16% versus 14%, 33% versus 28% and 45% versus 50% at 1, 2 and 5 years respectively. There was a significant difference in the cumulative discontinuation rates due to amenorrhoea in the two groups (2.6% versus 0%, 10.7% versus 0% and 13% versus 0% at 1, 2 and 5 years respectively). The data for the cumulative discontinuation rates due to other menstrual problems and pain were 6.5% versus 3.5%, 7.5% versus 7.1% and 8.3% versus 21.7% at 1, 2 and 5 years respectively.[147-150][EL=1+]

One European multicentre RCT which compared IUS-20 (n=1821) and Nova T IUD (n=937) (copper surface 200) reported discontinuation rates of 20% versus 17%, 34% versus 29%, 43% versus 41%, 49% versus 49% and 53% versus 56% at 1, 2, 3, 4 and 5 years. The cumulative rate for removal due to amenorrhoea was significantly higher in users of IUS-20 than Nova T (1.5% versus 0%, 2.9% versus 0%, 3.6% versus 0%, 4.2% versus 0% and 4.3% versus 0% at 1, 2, 3, 4 and 5 years). The cumulative rate for removal for other bleeding problems and pain were 7.4% versus 7.3%, 11.1% versus 11.6%, 13% versus 15.3%, 14.2% versus 18.1% and 15.1% versus 20.4% at 1, 2, 3, 4 and 5 years respectively. The cumulative rates for removal due to PID were 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5%, and 0.6% versus 1.6% respectively. Significant differences were also reported in removal rates between IUS and IUD due to depression (2.9% versus 0%), acne (2.3% versus 0.4%), headache (1.9% versus 0.25) and weight change (1.5% versus 0%) at 5 years.[151-154][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rates of 30%, 43%, 51%, 56% and 60% at 1, 2, 3, 4 and 5 years. The corresponding figures for IUS removal due to bleeding problems (excluding amenorrhoea) were 10.5%, 12.6%, 13.7%, 14.7% and 16.7%; due to pain (2.3%, 3.5%, 3.5%, 4.3% and 4.3%) and due to PID (0.9%, 1.2%, 1.2%, 1.2% and 1.2%) at 1, 2, 3, 4 and 5 years. There were 26 IUS removals due to oligoamenorrhoea at 5 years (3.8%). The average length of use before removal of IUS for bleeding problems was 11.7 months. Removals due to premenstrual symptoms were 14; mood swings/depression (13), loss of libido (5), headaches/migraine (9) and acne (7) at 5 years. There were 96 women lost to follow-up at 5 years.[241][EL=3]

A Finnish cross-sectional survey (n=17914) reported discontinuation rates of 7%, 13%, 19%, 25% and 35% among LNG-IUS users at 1, 2, 3, 4 and 5 years. There was a significant association between bleeding problems and the premature removal of LNG-IUS (RR 2.77; 95% CI 2.51 to 3.07). Removal was significantly lower in women who had an occasional or total absence of

menstruation. (RR0.46; 95% CI 0.43 to 0.50) The relative risk of premature removal of LNG-IUS due to pelvic infection was 1.40 (95% CI 1.25 to 1.57), due to pain (RR 1.32, 95% CI 1.23 to 1.42), depression (RR 1.33, 95% CI 1.24 to 1.43) and recurrent vaginal infections (RR 1.25, 95% CI 1.14 to 1.38).[242][EL=3].

One non-comparative study (n=165) in Austria reported a cumulative discontinuation rate of 10% among LNG-IUS users at 3 years. The main reason for discontinuation was bleeding problems (19%), reduced libido (13%) and other side effects such as skin problems, weight gain, depressive moods and ovarian cysts (31%). [79][EL=3] Another non-comparative study (n=203) in France reported a cumulative discontinuation rate of 11% among LNG-IUS users at 1 year. The main reason for discontinuation was bleeding problems (48%), pain (22%) and hormonal side effects (13%).[243][EL=3]

Summary of evidence

Table 5.3 LNG-IUS vs copper IUDs: discontinuation rates %

	Discontinuation rates %					
Studies	**Reasons for removal**	**TCu380A (licensed 8 years**	**Nova-T 200 (no longer licensed)**	**LNG-IUS (licensed 5 years)**	**Rate measured at point (year)**	**EL**
153 154	**Overall**		17	20	1	1+
			41	43	3	
			56	53	5	
148 149 150			14	16	1	1+
			28	33	2	
			50	45	5	
142 143 144		18		24	1	1+
		41		51	3	
		67		60	5	
		72		77	7	
241				30.0	1	3
				51.0	3	
				60.0	5	
242				7	1	3
				19	3	
				35	5	
153 154	**Amenorrhoea**		0.0	1.5	1	1+
			0.0	3.6	3	
			0.0	4.3	5	
148 149 150			0.0	2.6	1	1+
			0.0	10.7	2	
			0.0	13	5	
142		0.1		4.9	1	1+

143 144		0.2		8.4	2	
		0.4		19.7	5	
		1.1		24.6	7	
131 132		0.5		23.5	6-7	1+
241				3.8	5	3
153 154	**Bleeding and pain**		7.3	7.4	1	1+
			15.3	13	3	
			20.4	15.1	5	
148 149 150			3.5	6.5	1	1+
			7.1	7.5	2	
			21.7	8.3	5	
142 143 144		7.0		6.0	1	1+
		11.3		8.6	2	
		23.0		15.4	5	
		30.0		20.4	7	
131 132		11.0		36.0	6-7	1+
241				10.5	1	3
				13.7	3	
				16.7	5	
153 154	**PID**		0.4	0.3	1	1+
			1.5	0.5	3	
			1.6	0.6	5	
142 143 144		0.8		0.9	1-2	1+
		1.2		1.4	3-5	
		1.5		1.6	6-7	
131 132		0.1		0.3	6-7	1+
241				0.9	1	3
				1.2	3	
				1.2	5	

- **The overall discontinuation rate was over 60% for both IUD and IUS users at 5 years.**
- **Discontinuation due to amenorrhoea was about 25% at 5 years among LNG-IUS users, 1% in IUD users at 5-6 years.**
- **Discontinuation due to bleeding/pain was about 16% in LNG-IUS users and 24% in IUD users at 5 years.**
- **The rate for discontinuation due to PID was under 1% at 5-6 years.**

Recommendations:

Health professionals and women should be made aware that up to 60% of women will stop using the IUS within 5 years. The most common reasons for discontinuation are unacceptable vaginal bleeding and pain. [C]

The less common reasons for discontinuation are:

- **hormone-related (non-bleeding)**
- **pelvic inflammatory disease. [C]**

5.5 Adverse effects

5.5.1. Bleeding problems

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported that LNG-IUS (n=1125) users were more likely to experience amenorrhoea than TCu380A IUD users (n=1121) at 3 months (RR 2.15; 95% CI 1.31 to 3.56) and at 3 years (RR 7.24; 95% CI 4.14 to 12.65). No significant differences were noticed between the two groups in terms of prolonged bleeding at 3 months and 1 year. For LNG-IUS users, amenorrhoea, spotting, menorrhagia, dysmenorrhoea and premenstrual syndrome all occurred at a significantly higher incidence in the first 2 years after insertion than at 3 and 4 years. The incidence of these bleeding disturbances declined further at 6 years and later years. Women aged 30 or over using LNG-IUS were significantly less likely to complain of amenorrhoea, scanty bleeding and dysmenorrhoea than were younger women.[141][EL=1+]

One European multicentre RCT which compared IUS-20 (n=1821) and Nova T IUD (n=937) (copper surface 200) reported 2.7% of Nova T users and 16.8% of LNG-IUS users experienced a period of at least 90 days' amenorrhoea at 1 year.[151-154][EL=1+]

Re-analyses of menstrual diaries (n=287) from one RCT[152] investigated bleeding patterns in women with post-abortal and post-menstrual insertion of Nova-T IUD (copper surface 200) and the LNG-IUS. Women having the LNG-IUS inserted post-abortally reported fewer bleeding days than women receiving it post-menstrually. Nova-T IUD users had more bleeding days than LNG-IUS users. The removal of the superficial endometrium during termination of pregnancy may result in these improved bleeding patterns.[157][EL=1+]

One non-comparative study (n=165) in Austria reported that cessation of menstruation occurred in 47% of women and over 80% of whom considered this to be a positive change. [79][EL=3]

Summary of evidence

- **Amenorrhoea is more likely to occur in IUS users than copper IUD users.**

Management of bleeding problems

We did not identify any studies which addressed this question. However, contraceptive counselling to provide information about the possibility of amenorrhoea will be beneficial. (See 3.5)

Recommendation:
Women may be advised that oligoamenorrhoea or amenorrhoea is highly likely to occur by the end of the first year after LNG-IUS insertion. However, persistent bleeding and spotting are common for the first six months. [D/GPP]

(Refer to contraceptive counseling 3.5)

5.6 Common concerns and symptoms

5.6.1 Weight change

Weight fluctuation in women of reproductive age is common, whether or not hormonal contraceptives are used.

An European RCT reported no evidence of a difference in body weight

change among women using the copper releasing Nova-T (copper surface 200)(n=937) or the hormone releasing LNG-IUS (n=1821). In this study, the mean weight at baseline was 61.6 (SD 10.6) kg in the Nova-T group and 62.0 (SD 10.0) kg in the LNG-IUS group. The mean weight had increased to 64.4 kg in both groups at 5 years (a mean increase of 2.5 kg in the Nova T group versus 2.4 kg in the LNG-IUS group). Removal of the device due to weight gain was however significantly different between LNG-IUS (1.5%) and IUD users (0%).[152][EL=1+]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a significant difference in subjective report of weight gain (0.7% in the LNG-IUS group versus 0.4% in the IUD group), but no difference in the discontinuation rate due to weight gain or weight loss over the 7 years.[141][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported 16 removals of IUS due to weight gain at 5 years.[241][EL=3]

Summary of evidence

- **Whilst removals for reported weight gain were higher in LNG-IUS users than IUD users, there is no evidence that LNG-IUS causes weight gain to a different degree than is associated with IUDs.**

Recommendation:

Women should be informed that there is no evidence that the LNG-IUS causes weight gain. However, some women discontinue the method citing weight gain as the reason, which may have occurred during the time of use as an unrelated event. [C]

5.6.2 Altered mood and libido

The experience of sexual dysfunction, such as loss of libido, is common among young women, ranging from 5 -10% in one literature review[167] to

about 30% in a national survey in the USA.[168]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a significant cumulative discontinuation rate due to depression of 2.9 vs 0% among LNG-IUS users and Nova-T users respectively at 5 years. It was not clear if the occurrence of depression was subjectively reported by the women or objectively measured by the investigators.[152][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported 14 and 13 removals due to premenstrual symptoms and mood swings/depression respectively at 5 years. There were 96 women lost to follow-up at 5 years.[241][EL=3]

Summary of evidence

Altered mood and libido were not increased in users of LNG-IUS compared with users of the IUD.

One RCT showed higher rate of discontinuation of IUS vs IUD due to depression at 5 years.

Recommendation:

Users of the LNG-IUS should be reassured that there is no increase above background prevalence in loss of libido or depression. [C]

5.6.3 Acne

Skin conditions, particularly acne, are common among young women. Progestogen only contraceptives, particularly the more androgenic progestogens like LNG, tend to increase sebum production which makes the skin greasier and prone to acne.[244]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a significant difference in the occurrence of acne (1.0% in the LNG-

IUS group versus 0.5% in the TCu380A IUD group) but discontinuation due to acne was not significant (0.1 vs 0.0)[141][EL=1+]

One European RCT comparing LNG-IUS with Nova-T IUD (copper surface 200) reported a non-significant cumulative discontinuation rate due to acne of 2.3 vs 0.4% among LNG-IUS with Nova-T IUD users respectively at 5 years (RR 5.56; 95% CI 0.73 to 42.35). However, a subjective reported side effect of acne was significantly higher among LNG-IUS users (3.5 vs 0.4%) at 3 months and was not significantly different between the two groups at 5 years (1.8 vs 0.3%).[152][EL=1+].

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported seven removals due to acne at 5 years. There were 96 women lost to follow-up at 5 years. [241][EL=3]

Summary of evidence

- **In a European RCT, discontinuation due to reported acne was 5 times higher among IUS users than IUD users at 5 years but this did not reach statistical significance. There was initial increased subjective reporting of acne, which was not noted at 5 years.**
- **Data from one RCT showed a significant increase in acne in the LNG-IUS group, but the discontinuation rate due to acne was not significant between the two groups.**

Recommendation:

Women should be informed that they may be at a theoretically increased risk for developing acne due to absorption of the progestogen, but that women do not discontinue the LNG-IUS for this reason frequently. [C]

5.6.4 Headache and migraines

Headache is one of the commonest symptoms experienced in the general population, both in young people and in adults. About 70% of adults report

headache in the previous 3 months; the prevalence is greater in females than in males.[245]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a statistically significant difference in the occurrence of headache (8.3% in the LNG-IUS group versus 4.3% in the TCu380A IUD group) at 7 years.[141][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported nine removals due to headaches/migraine at 5 years. There were 96 women lost to follow-up at 5 years.[241][EL=3]
In the current WHOMEC recommendations, the LNG-IUS is assigned category '2' for initiation and category '3' for continuation in women who have migraine with focal symptoms at any age. Any new headaches or marked changes in headaches should be evaluated.[16][EL=1-4]

Summary of evidence

- **Headache incidence increases with LNG-IUS use.**

Recommendation:
Women should be informed that all progestogen-only methods, including the LNG-IUS, may be used by women who have migraine with or without aura. However, if the aura becomes more severe or frequent, the headaches should be investigated and alternative methods of contraception considered. [D/GPP]

5.7 Risks

5.7.1 Cardiovascular disease

We did not identify any studies which assessed the risks of cardiovascular disease associated with the use of LNG-IUS.

In the current WHOMEC, IUS are assigned category '2' for women with valvular heart disease. WHOMEC recommends that prophylactic antibiotics be used at time of insertion to prevent endocarditis.[16]

A small study identified transient bacteraemia from vaginal organisms in 13% of women within 10 minutes of IUD replacement/insertion.[171][EL=3]

In the current WHOMEC recommendations, LNG-IUS is assigned category '2' for women with a history of deep vein thrombosis and pulmonary embolism and category '3' for women with current deep vein thrombosis and pulmonary embolism.[16][EL=1-4]

Recommendation:

Women with a history of venous thromboembolism (VTE) may use LNG-IUS. [D/GPP]

Women with a current VTE are advised not to use LNG-IUS. [D/GPP]

5.7.2 Bone mineral density

We did not identify any studies which addressed this question.

5.7.3 Ectopic pregnancy

An ectopic pregnancy refers to any pregnancy that occurs outside the uterus. The absolute risk of ectopic pregnancy (ie, the risk that a woman will experience an ectopic pregnancy) is a function of the absolute risk of pregnancy in combination with the conditional risk of ectopic pregnancy (ie, the risk that a pregnancy will be ectopic). All methods of contraception decrease the risk of ectopic pregnancy as they reduce the absolute risk of pregnancy. The *relative* likelihood of a pregnancy being ectopic is greatly increased when a woman becomes pregnant during use of an IUD.[172] It is estimated that 1.4 per 100 pregnancies in women using no contraception is

likely to be an ectopic pregnancy. The ectopic pregnancy rate in women generally increases with age.

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported 0 versus 2 ectopic pregnancies in LNG-IUS and TCu380A users respectively at 7 years.[141][EL=1+]

One European multi-centre RCT compared IUS-20 (n=1821) and Nova T IUD (n=937). The ectopic pregnancy rates were 0.02% versus 0.25% in the IUS and Nova T groups respectively during the 5 year period.[152][EL=1+]

Interim results from the WHO international muticentred RCT (n=3815 insertions) reported a significant difference in ectopic pregnancy rate among LNG-IUS and TCu380A IUD users at and after 6 years (0 versus 0.1). [131;132][EL=1+]

A cross-sectional survey of 17,360 users of LNG-IUS reported the outcome of pregnancy during LNG-IUS use. One hundred and thirty-two pregnancies were reported and 108 medical records were reviewed. In 64 pregnancies, conception occurred with the LNG-IUS in situ. Thirty-three pregnancies were ectopic.[246][EL=3]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported one ectopic pregnancy at 5 years.[241][EL=3]

The LNG-IUS is assigned category ‘1’ for women with past ectopic pregnancy in the current WHOMEC recommendations. When a woman becomes pregnant during IUD use, the relative likelihood of ectopic pregnancy is increased.[16][EL=4]

Summary of evidence

- **Ectopic pregnancy rates from 0 to 0.1% were reported in users of LNG-IUS.**

- **LNG-IUS users have lower ectopic pregnancy rates than IUD users but this not clinically significant.**

Recommendations:

Women with a history of previous ectopic pregnancy are at increased risk of future ectopic pregnancies. Women who become pregnant with a LNG-IUS in place should have intrauterine and ectopic pregnancy excluded. [D/GPP]

Women should be advised that in the event of a LNG-IUS failure the risk of ectopic pregnancy is less than 0.1%. [C]

5.7.4 Actinomyces-like organisms

Actinomyces israelli are commensal bacteria of the female genital tract. Actinomyces-like organisms (ALOs) are found in women with and without an IUD.[176-179] The role of actinomyces-like organisms in infection in IUD users is unclear.[180] They may be identified on cervical smears, but have not been shown to be predictive of any disease.[120;181-183] IUDs users may have a higher risk of infection with actinomyces-like organisms compared to non-users.

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a similarly low incidence of actinomyces on cervical smears (0% versus 0.1%) in both the LNG-IUS and the TCu380A IUD groups.[141][EL=1-]

A Swiss study of 156 women found the incidence of actinomyces-like organisms to be significantly higher among women using Multiload Cu375 than women using LNG-IUS (20% versus 2.9% at 22 months of follow-up).[185][EL=3] However, differences between the prevalence rates may be attributable to cervical sampling and staining techniques, population characteristics and the potential for bias associated with retrospective reviews of case notes.

Recommendation:
The presence of actinomyces-like organisms on a cervical smear in a woman with a current LNG-IUS requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. [D/GPP]

5.7.5 Pelvic inflammatory disease

A major cause of pelvic inflammatory disease (PID) is Chlamydia trachomatis, a sexually transmitted infection of the genital tract. PID results in chronic abdominal pain, ectopic pregnancy and can lead to tubal factor infertility. [187] Chlamydia trachomatis is the most common STI in the UK and Europe, present in 11% of the sexually active population aged 19 or younger.[188][EL=3] Asymptomatic chlamydial infection can only be detected by screening. Uterine instrumentation carried out as part of insertion may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic pelvic inflammatory disease. The Chief Medical Officer 's Advisory Group on Chlamydia recommends that opportunistic screening of any woman undergoing instrumentation of the uterus be considered because of a resultant risk of ascending infection.[189][EL=4]

The annual incidence of PID is estimated to be 1-2% in women of reproductive age in the US.[190]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu380A users in discontinuation rate due to PID (0.9% versus 0.8% ,1.4% versus 1.2%, and 1.6% versus 1.5% at 1-2, 3-5 and 6-7 years respectively).[141-145][EL=1+]

One European multicentre RCT which compared IUS-20 (n=1821) and Nova T IUD (n=937) (copper surface 200) reported cumulative rates for removal due to PID were 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%,

0.5% versus 1.5%, and 0.6% versus 1.6% at 1, 2, 3, 4 and 5 years respectively. [151-154][EL=1+]

Interim results from the WHO international multicentred RCT (n=3815 insertions) showed no significant difference in discontinuation rates due to PID between LNG-IUS users (n=464) and TCu380A IUD users (n=580) at and after 6 years (0.3 versus 0.1).[131][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rate due to PID of 0.9%, 1.2%, 1.2%, 1.2% and 1.2% at 1, 2, 3, 4 and 5 years respectively.[241][EL=3]

In the current WHOMEC recommendations, LNG-IUS is assigned category '1' for initiation and continuation in women with past PID with subsequent pregnancy, category '2' for initiation and continuation in women with past PID without subsequent pregnancy, and category '4' for initiation in women with current PID.[16][EL=1-4]

Summary of evidence

- **The risk of PID in users is low.**
- **Removal due to PID among IUS users is below 1% at 1 year , and below 1.5% at 5 years.**

Recommendations:

Women should be informed that the chance of developing PID following LNG-IUS insertion is very low in women at low risk of sexually transmitted infections, at less than 1% over 1 year. [C]

All women should be offered screening for STIs before LNG-IUS insertion and women at risk of STIs should be strongly encouraged to accept the offer. [D/GPP]

Where screening is not possible, or where screening has not been completed, use of prophylactic antibiotics is recommended in women with increased risk of STIs. [D/GPP]

5.7.6 Uterine perforation

Uterine perforation occurs in fewer than 1 in 1000 insertions of IUDs.[118;197]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a similarly low discontinuation rate due to uterine perforation (0.1% versus 0%) and cervical perforation (0% versus <0.1%) between the LNG-IUS users and TCu380A users at 7 years.[141][EL=1+]

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported no perforation after 5 years of use.[241][EL=3]

Another non-comparative study (n=3452) reported three uterine perforation with LNG-IUS (0.9 per 1000 insertions) at 3 years.[247][EL=3]

Summary of evidence

- **Uterine perforation associated with IUD and LNG-IUS use is low : less than 1%.**

Recommendations:

Women should be reassured that the risk of uterine perforation at the time of LNG-IUS insertion is very low at approximately 1 in 1000 over 5 years. [C]

Women should be advised on symptoms of uterine perforation, which would warrant an early review. [D/GPP]

Women should be informed that the risk of perforation is related to the skill of the clinician inserting the device. [D/GPP]

5.7.7 Women who become pregnant while using the IUS

We did not identify any studies. However, the UKSPR comments that if the pregnancy continues, there may be added risks to the foetus due to the hormonal exposure. (Refer to section 5.7.3 for recommendations on ectopic pregnancy)

Recommendations:
Women who become pregnant with the LNG-IUS in situ should be advised to consult early to exclude ectopic pregnancy. [D/GPP]

If the pregnancy is before 12 weeks and the LNG-IUS can be easily removed, it should be removed regardless of the woman's intentions to continue or terminate the pregnancy. [D/GPP]

5.8 Return to fertility

A multinational European RCT compared the recovery of fertility between ex-users of LNG-IUS (n=139) and Nova T (n=71) (likely to be formerly Novagard, copper surface 200, discontinued in 2001). There was no significant difference in cumulative conception rates between ex-LNG-IUS users and ex-Nova-T users (79.1% versus 71.2%) at 1 year and 86.6% versus 79.7% at 2 years. Ninety-six percent of the pregnancies occurred during the first year after removal and 84% of the pregnancies in the Nova-T group and 86% in the LNG-IUS group ended in live births.[154][EL=1+]

Another RCT reported a pregnancy rate of 96.4% in ex-LNG-IUS users (n=60) compared to 91.1% in ex- TCu380A IUD users (n=50) at 1 year.[146;206][EL=1+]

A cohort study comparing pregnancy rates after cessation of use of LNG-IUS (n=91), TCu380A (n=103) and Norplant (n=62) reported pregnancy rates of 88%, 88% and 87% in these three groups at 2 years. For all groups, pregnancy rates were higher in women under 30 years of age.[248][EL=2]

A questionnaire survey of pregnant women (n=2841) in the UK evaluated the impact of contraceptive methods on subsequent fecundity. It reported that all LNG-IUS users (n=13) conceived within one month after discontinuation. [207][EL=3] (see 4.8.2, 6.7.3 and 7.7.2)

Summary of evidence

- **Between 79% and 96% of women had achieved conception by 1 year after removal of LNG-IUS.**

Recommendation:

Women should be informed that there is no evidence for any delay in return of fertility following removal or expulsion of the LNG-IUS. [C]

5.9 Details of method use

5.9.1 Assessment prior to fitting

(See 3.6)

All women considering the use of LNG-IUS should be assessed as outlined for the IUD.[199] These include bimanual pelvic examination, testing for STIs if indicated, measurement of pulse and blood pressure, prophylaxis to prevent pelvic infection if indicated, and prophylaxis to prevent bacterial endocarditis in those at risk. Women with an identified risk of STI should have their decision on their chosen method of contraception reviewed and alternative methods should be discussed.

WHOMEC recommends that LNG-IUS should not be inserted when a woman has PID, or an STI, currently or within the last 3 months.[16] The FFPRHC recommends that, as for IUD insertion, after considering other contraceptive methods, a woman may use the LNG-IUS within three months of treated pelvic infection, provided she has no signs and symptoms.[199]

Recommendations:

Healthcare professionals fitting a LNG-IUS should have reasonably excluded relevant genital tract (cervical or pelvic) infection (chlamydia, gonorrhoea and PID) by assessing sexual history, clinical examination and if indicated, by appropriate laboratory tests. [D/GPP]

Women with identified risks associated with uterine or systemic infection should have an investigation, appropriate prophylaxis or treatment instigated prior to insertion of the LNG-IUS. [D/GPP]

5.9.2 Information prior to insertion

(See 3.5)

Recommendations:

Women should be advised of failure rates, benefits, risks and side effects of the LNG-IUS. [D/GPP]

Women should be informed that the insertion of a LNG-IUS may cause pain and discomfort for a few hours and light bleeding for a few days following insertion and should be advised about appropriate pain relief. [D/GPP]

5.9.3 Position within the uterine cavity

We found no evidence that assessed the effect of the position of IUD within the uterine cavity.

Recommendation:

Women should be informed that the effect of the position of a LNG-IUS within the uterine cavity, in relation to contraceptive efficacy, is not known. [D/GPP]

5.9.4 Time of fitting of the LNG-IUS

In a normal menstrual cycle

It is important to check that the woman is not pregnant before fitting by taking a menstrual and coital history, and carrying out a pregnancy test if indicated.

The Summary of Product Characteristics (SPC) for the LNG-IUS recommends insertion within 7 days of the onset of menstruation (anytime if replacement) or immediately after the first trimester termination of pregnancy. The FFPRHC recommends that an LNG-IUS can be inserted at other times in the cycles if there has been no risk of pregnancy. In such situations additional contraception is required for seven days.[249]

When switching method

The UKSPR and the FFPRHC both recommend that the LNG-IUS can be inserted at any time if it is reasonably certain that the woman is not pregnant and other hormonal methods have been used consistently and correctly. Additional contraceptive protection is then required for the next 7 days.[249][EL=1-4]

Following termination of pregnancy

WHOMEC recommends the LNG-IUS be inserted immediately after surgical termination of pregnancy – first trimester or second trimester.[172] After medical termination of pregnancy, the insertion of the LNG-IUS should be performed at any time after the procedure is complete.[249]

One RCT compared LNG-IUS with Nova-T IUD inserted at time of elective termination of pregnancy. It reported significantly lower cumulative pregnancy rates (0.8 vs 9.5 per 100 women) but significantly higher cumulative discontinuation rates in LNG-IUS users due to hormonal reasons (15.9 vs 3.9 per 100 women) respectively at 5 years. [209][EI=1+]

Post delivery

We did not identify any studies. Advice regarding postpartum insertion of the LNG-IUS follows that for the IUD.[199] LNG-IUS is assigned category '1' for insertion at four or more weeks post-partum. [16][EL=1-4]

Recommendations:

A LNG-IUS can be inserted at any time during a menstrual cycle if it is reasonably certain the woman is not pregnant. [D/GPP]

A LNG-IUS can be inserted immediately or at any time following first and second trimester termination of pregnancy. [D/GPP]

A LNG-IUS can be inserted from 4 weeks post partum irrespective of the mode of delivery if it is reasonably certain the woman is not pregnant. Use before 6 weeks is outside the product license. [D/GPP]

5.10 Training of health professionals

(See 3.14)

We did not identify any studies. Advice regarding training follows that for IUDs. A large prospective study, which included 17,469 Multiload Cu375 insertions by 1,699 doctors, reported an incidence of 1.6 uterine perforation per 1000 insertions at 6 years. Doctors who reported performing fewer than 10 IUDs insertions in the 6-year period reported significantly more perforations than doctors who performed between 10 to 49 IUD insertions (RR 2.3; 9%% CI 0.99 to 5.26) and doctors who performed between 50 to 99 IUD insertions (RR 7.3; 95%CI 0.94 to 56.3) in the same study period.[197][EL=2+]

A secondary analysis of TCu380A acceptors from one RCT in three developing countries compared insertion failures and complications between non-physician (n=174) and physician insertions (n=193). It reported an overall significantly higher cumulative discontinuation rate due to expulsion (8.6% vs

2.7%), bleeding/pain (8.1% vs 1.4%). The over all continuation rate was lower (77.3% vs 85.5%) at 12 months. This suggested that appropriate competency-based training is required to limit the number of expulsions and removals for bleeding and pain by non-physicians.[218][EL=2+]

A cohort study compared IUD insertions by specialist nurses (n=22) and doctors (n=28). It reported that adequately trained nurses were proficient and safe at IUD insertions, regardless of the woman's parity.[219][EL=2-]

A systematic review of framed and frameless IUDs suggested that skills of the health professionals appeared to play a part in the expulsion and pregnancy rates of the frameless devices. [140][EL=1++] A narrative review reported that the performance of IUDs in comparative trials are often reflective of operator skills and quality of care and follow-up, rather than the nature of the device studied. [220][EL=3] IUD expulsion rates were reported to be significantly higher for inexperienced inserters. [221]EL=1+]

The FFPRHC has specific training requirements for doctors wishing to obtain a letter of competence (LOC) in intrauterine techniques (IUT). Competence in gynaecological examination and the assessment, management and investigation of women with IUD problems are required for all health professionals inserting IUDs. Recertification should ensure continuing competence. The letter of competence (LoC) must be updated every five years, with at least 2 hours of relevant continuing education and a log of at least 12 insertions in 12 months or six in 6 months using at least two different types of device in unanaesthetised patients.

The Royal College of Nursing Sexual Health Forum has issued training guidance and requirements for nurses wishing to insert IUDs.[105][EL=4] It outlines eligibility criteria for adequate training (for example, obtain a recognised family planning/contraception qualification) and the knowledge and skills required to perform insertion and explain various aspects of care. Nurses can receive training from experienced doctors with a letter of competence in intrauterine techniques (LoC IUT). Nurses must also observe a

minimum of five insertions, and fit a minimum of ten devices of varying types.

Recommendation:
IUDs should only be fitted by trained personnel with continuing experience of fitting at least one copper IUD or one LNG-IUS a month. [D/GPP]

5.11 Specific groups

Adolescents

We did not identify any studies which assessed the use of LNG-IUS in adolescents.

One RCT (n=200) compared LNG-IUS and COC use among young nulliparous women aged 18-25. It reported no pregnancies or PID in either groups at 1 year. There was one partial expulsion in the IUS group at 6 months. The discontinuation rates due to pain were 6.7% vs 0%, due to bleeding (2.5% vs 0%), due to spotting (0% vs 1.25%). The overall discontinuation rate was 20% vs 27% at 1 year. [250][EL=1+]

LNG-IUS is assigned category '2' for women under 20 years.[16] However, WHOMEC comments that there is concern both about the risk of expulsion due to nulliparity and the risk of STIs due to patterns of sexual behaviour in younger age groups.

Women over 40 years of age

A non-comparative study (n=203) in France reported no pregnancy, expulsion and no perforation among LNG-IUS users aged 35-45 at 1 year. The cumulative discontinuation rate was 11%. The main reason for discontinuation was bleeding problems (48%), pain (22%) and hormonal side effects (13%) at 1 year.[243][EL=3]

Recommendations:

LNG-IUS may be inserted in adolescents. However, STI risk and Fraser competence should be considered. [D/GPP]

Women should be informed that nulliparity at any age is not a contraindication to LNG-IUS insertion. [D/GPP]

Women should be informed that those of all ages can use LNG-IUS. [D/GPP]

Women with body mass index over 30

We did not identify any studies. LNG-IUS is assigned category '1' for women with BMI> 30kg/m^2 in the current WHOMEC recommendations.[16]

Women who are breastfeeding

A cross sectional study (n=11) reported low concentrations of LNG in breast milk.[251][EL=3] It has been recommended that women who are breastfeeding, and who are four or more weeks postpartum may choose the LNG-IUS.[249] LNG-IUS is assigned category '1' for women who are beyond four weeks postpartum and breastfeeding.[16]

Recommendation:

Women should be informed that LNG-IUS can be safely used by breast feeding mothers. [D/GPP]

5.12 Medical conditions and contraindications

Diabetes

LNG-IUS is assigned category '2' for women with non-insulin dependent and insulin-dependent diabetes in the current WHOMEC recommendations. Whether the amount of LNG released may influence carbohydrate and lipid

metabolism is not clear.[16]

Recommendation:
Women should be informed that diabetes poses no restriction to use of LNG-IUS. [D/GPP]

Epilepsy

There is no evidence that the medical condition of a woman with epilepsy is altered by the presence of a LNG-IUS. However, there may be increased risk of a fit being precipitated during the insertion procedure.

LNG-IUS is assigned category '1' for women with epilepsy in the current WHOMEC recommendations.[16]

Recommendation:
Emergency drugs including anti-epileptic medication should be available at the time of fitting a LNG-IUS in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation. [D/GPP]

Sexually transmitted infections, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)
(See 3.11)

We did not identify any studies which addressed the use of LNG-IUS in women with HIV/AIDS. Please refer to Chapter 4 on IUDs.

In the current WHOMEC recommendations, LNG-IUS is assigned category '2' for initiation and continuation for women who are at high risk of HIV and who are HIV-infected. For women with AIDS, LNG-IUS is assigned category '3' for initiation and category '2' for continuation. For women who are clinically well on anti-retroviral therapy, LNG-IUS is assigned category '2' for both initiation and continuation.[16]

Summary of evidence

- **No evidence was identified of increased incidence of PID or increased rate of transmission of HIV to partners during the use of LNG-IUS.**

Recommendation:
The LNG-IUS is a safe and effective method of contraception for women who are HIV positive or have AIDS. Safer sex using condoms should also be encouraged. [D/GPP]

5.13 Drug interactions

Data from an ongoing survey have not identified any reduction in the efficacy of LNG-IUS with liver enzyme-inducing drugs.[252][EL=3] LNG-IUS is assigned category '1' for women who are prescribed drugs which affect liver enzymes, such as rifampicin and anti-epileptic drugs.[16]

Levonorgestrel is released directly into the uterine cavity with LNG-IUS, and contraceptive effects are mainly local and, therefore, not affected by the presence or absence of enzyme-inducing epileptic medication.[253][EL=2-3] LNG-IUS is assigned category '1' for women who are prescribed antiepileptic drugs.[16].

Antibiotics

In the current WHOMEC recommendations, LNG-IUS is assigned category '1' for women who are prescribed antibiotics.[16]

Recommendation:
Women and health professionals should be made aware that there is no evidence of reduced effectiveness of LNG-IUS when taking any other medication. [D/GPP]

5.14 Follow-up

We did not identify any studies. The UKSPR recommends a follow-up visit 3-6 weeks after insertion for IUD users.[78][EL=1-4]

Recommendation:
A follow-up visit should be carried out after the first menses, or 3 to 6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be advised to return at any time to discuss problems, if she wants to change her method, or when it is time to have the LNG-IUS removed. [D/GPP]

5.15 Economic evidence

The economic analysis carried out for the guideline demonstrated that IUS is more effective and less costly than male condom and COC (i.e. it dominates male condom and COC), starting from 2 years of contraceptive use and above. For one year of use, IUS is more effective but also more costly than the male condom and the COC, at an additional cost of £437 and £513 per pregnancy averted, respectively.

Over all, non-reversible contraceptive methods are more effective than IUS; lower overall effectiveness for IUS (translated into higher number of unintended pregnancies due to contraceptive failure) is explained by the high discontinuation rates characterising all LARC methods. On average, this leads to the use of less effective contraceptive methods. For short periods of contraceptive use, male and female sterilisation are also more costly than IUS. However, in total, they become less costly than IUS at 4 and 6 years of contraceptive use respectively. Starting from these time frames and above, non-reversible contraceptive methods dominate IUS.

IUS dominates the injectable for contraceptive use equal to 2 years and up to 15 years (this being the maximum time horizon considered in the analysis). For one year of use, IUS is more effective than the injectable, but at an additional cost of £5,100 per additional pregnancy averted.

The IUS is dominated by IUD for 2 and up to 4 years of use. For longer periods of use, IUS is more effective than IUD, but at an additional cost. The Incremental Cost Effectiveness Ratio (ICER) of IUS compared to IUD generally tends to decrease over time, although a small increase is observed at 11 years of use, due to costs of IUS re-insertion after 10 years of use. The additional cost of IUS compared to IUD starts from £18,845 per pregnancy averted for 5 years of use, and falls at £1,884 per pregnancy averted at 15 years of use. For one year of use, the IUS is also more effective and more costly than the IUD, with an ICER of £60,322 per pregnancy averted.

The IUS is dominated by the implant for short periods of use, up to 3 years, and also for 6 years of use. For the other time-frames examined, the implant is both more effective and more costly than the IUS, with ICERs ranging between £12,229 per pregnancy averted at 4 years of use and £741 per pregnancy averted at 12 years of use, depending also on the times of re-insertion of the two methods.

The relative cost-effectiveness of IUS to IUD and the implant is highly affected by discontinuation rates associated with LARC use.

Evidence statement

- **IUS is more cost-effective than male condom and COC, even for short periods of contraceptive use (1-2 years).**

- **Male and female sterilisation are more cost-effective than IUS for longer duration of contraceptive use, i.e. 4 and 6 years respectively.**

- **IUS is more cost-effective than the injectable between 2 and 15 years of contraceptive use. IUS is less cost-effective than the implant for periods of use between 1-3 years, and also for 6 years of use. It is also less cost-effective than IUD for periods of use between 2-4 years. Nevertheless, relative cost-effectiveness between IUS and other LARC methods, in particular IUD and the implant, is significantly affected by the level of discontinuation associated with LARC use.**

1 Full results of the economic analysis are presented in chapter 8.

6. Progestogen-only injectable contraceptives (POICs)

6.1 Introduction

6.1.1 What they are

Progestogen-only injectable contraceptives (POICs) are slow-release preparations lasting several weeks. DMPA (depot medroxyprogesterone acetate) and NET-EN (norethisterone enanthate) are the two progestogen-only injectable contraceptives available in the UK. DMPA is licensed as a first-line contraceptive for long-term and short term use. NET-EN is licensed for short-term use (up to two injections) by women whose partners undergo vasectomy, until the vasectomy is effective, and by women immunized against rubella, to prevent pregnancy until immunity develops.

Erosion of the drug from the surface of the DMPA microcrystals provides a slow release and a subsequent prolonged action. Injection of NET-EN in its castor oil/benzyl benzoate vehicle is followed by partial hydrolysis of the ester to the active compound norethisterone.[254]

DMPA is an aqueous suspension available in a pre-filled syringe which should be thoroughly mixed before use to ensure complete suspension of the contents. NET-EN is a thick oily fluid which is drawn up into a syringe; the ampoule should be immersed in warm water before use to decrease the viscosity. Both preparations are given by intramuscular injection: DMPA at a dose of 150 mg (in 1mL) every 12 weeks and NET-EN 200 mg (in 1mL) every 8 weeks. With each there is a sharp rise in progestogen blood concentration over one to two days, followed by a gradual decline over the following weeks. A new micronised formulation of DMPA has been developed, to be given subcutaneously every 12 weeks. While delivering a 30% lower total dose than the intramuscular formulation (104 mg), the SC formulation suppressed ovulation for more than 13 weeks in all subjects and was not affected by body mass.[255]

6.1.2 Mechanism of action

Both DMPA and NET-EN prevent pregnancy by the inhibition of ovulation and thickening the cervical mucus, thereby presenting a barrier for sperm penetration. In addition, changes to the endometrium make it an unfavourable environment for implantation.[256-259]

Recommendation:
Women should be advised that progestogen-only contraceptive injectables work primarily by preventing ovulation. [C]

6.1.3 Use in the UK

It is estimated that fewer than 3% of women aged 16-49 in Great Britain chose injectables as their method of contraception in 2003/4.[1][EL=3]

6.1.4 Duration of action

The ideal administration interval with NET-EN has been found to be 56 ± 7 days.[260] Longer intervals between NET-EN administrations is associated with higher pregnancy rates. Four pregnancies occurred in one study using 70 ± 7 days as the administration interval over 33 months. Another, administering NET-EN every 12 weeks over a 12 month period, resulted in a pregnancy rate of 0.1% to 0.6%.[256]

With POICs, progestogen blood concentrations remain consistently high enough to maintain contraceptive effect for three months post-injection with DMPA and two months with NET-EN.[261-263]

The time it takes for progestogen concentrations to be insufficient (i.e. to wear off) for contraception may vary from population to population.[264][EL=3]

Recommendation:
Depot medroxyprogesterone acetate (DMPA) should be repeated every 12 weeks and norethisterone enanthate (NET-EN) every 8 weeks. [C]

6.1.5 The evidence

Considering how widely used DMPA is worldwide, there is little published evidence of its safety, effectiveness and associated discontinuation rates. Asian and South American studies on weight changes have not been cited as the absolute weight of these populations is so different. (See 3.4)

6.2 Effectiveness

In a multinational RCT that compared DMPA (n=1587) with NET-EN (n=789), given at their licensed dosage intervals, the reported cumulative pregnancy rates were 0.1% versus 0.4% at 1 year, and 0.4% in both groups at 2 years.[265][EL=1+] For DMPA, these effectiveness rates have been confirmed in one multinational RCT (0.7% at one year)[266][EL=1+] and one cohort study (0.4% at one year), in which DMPA was given at the licensed interval with NET-EN given every twelve weeks.[267][EL=2+]

A cohort study in Kenya (n=1076) reported a pregnancy rate of 1.5% in CuT380A users, 2.1% in users of a COC, and 0.3% in DMPA users at 1 year.[155][EL=2+]

A US cohort study of adolescents living in inner-cities reported a cumulative pregnancy rate of 11% in DMPA users (n=111) versus 28% in COC users (n=50) at 1 year.[268][EL=2-]

Recommendation:
Women should be advised that injectable contraceptives, when given at the appropriate intervals, have very low pregnancy rates, no higher than 0.4 in 100 at 2 years. Pregnancy rates with DMPA are lower than those with NET-EN. [C]

6.3 Discontinuation and reasons for discontinuation

(See 3.10)

One multinational RCT (n=1216), undertaken mainly in developing countries, compared menstrual diaries in women given DMPA in 100mg and 150mg every three months. The cumulative discontinuation rate was 41% in both groups at 1 year, mainly due to bleeding problems (rates varied between centres ranging from 0 - 22%).[269][EL=1-]

Four non-comparative studies from the US demonstrated discontinuation rates among DMPA users ranging from 41% to 77% at 1 year. One study showed discontinuation rates up to 79% among DMPA users at 5 years. The main reasons for discontinuation were bleeding problems (8 - 30%) and weight gain (7 - 24%)[270-273][EL=3]

Two surveys conducted in New Zealand and Australia (n=252, mean no. of injections 8.7; n=363, mean no. of injection 6.3) reported discontinuation rates of 20% to 35% for bleeding disturbances and weight gain (8 -12%) among DMPA users. [274;275][EL=3]

A UK non-comparative study (n=707) reported cumulative discontinuation rates of 23.4%, 36.3% and 66.2% at 1, 2 and 3 years among NET-EN users. The main reasons for discontinuation were unacceptable menstrual bleeding (39%) and other method-related side effects (25%). [260][EL=3]

One multinational RCT reported similar discontinuation rates among DMPA (n=1587) and NET-EN (n=789) users (51% versus 50% at 1 year, and 74% versus 71% at 2 years). Apart from discontinuation for personal reasons (40%), the other reasons for discontinuation were around 20% for bleeding problems and between 15-25% for amenorrhoea at 2 years.[265][EL=1+]

A New Zealand cohort study (n=6262) reported discontinuation rates of 48%, 44%, and 42% among DMPA, IUD or COC users respectively at 2 years.

Personal reasons or changing to a 'definitive contraceptive method' were more common than medical reasons for discontinuation (28% vs 20% vs 35%). Discontinuation due to medical reasons,which included weight and bleeding problems,were 12% vs 16% vs 21%.[276][EL=2+]

A US cohort study (n=122) reported significantly lower discontinuation rates among postpartum adolescents using DMPA versus those using COC (45% versus 73%) at 1 year. The reasons for discontinuation due to disrupted menstrual cycle were 40% vs 4%, due to weight gain 12% vs 0% at 1 year. [277][EL=2+]

A cohort study reported similar discontinuation rates among postpartum adolescents using DMPA (n=111) or COC (n=50) at (66% versus 68% at 1 year). The primary reason for discontinuation was side effects which included bleeding problems and weight gain (79% DMPA versus 44% OC).[268][EL=2-]

An Australian case note review of DMPA discontinuers (n=247) reported that 42% had no further need for contraception, 10% experienced bleeding irregularities, and 9% desired pregnancy.[274][EL=3]

A US cross-sectional survey of adolescent users of DMPA (n=35) and Norplant (n=31) reported that the commonest reported reasons for discontinuation of DMPA were irregular bleeding (60%), weight gain (40%), increased headaches (26%), mood changes (20%), fatigue (20%), and loss of scalp hair (20%) at 1 year.[278][EL=3]

Summary of evidence

- **The overall discontinuation rate for all reasons among DMPA users is around 50% at 1 year.**
- **Discontinuation due to bleeding problems is between 30-40% among DMPA users.**

Recommendations:

Health professionals should know that as many as 50% of women using DMPA may discontinue by 1 year. [C]

Women should be informed that an altered bleeding pattern is a common reason for the discontinuation of use of DMPA. [C]

6.4 Adverse effects

We did not identify any studies which reported the incidence of anaphylactic reaction or death as a result of receiving DMPA or NET-EN injection.

6.4.1 Bleeding problems

Amenorrhoea is a predictable side effect of DMPA and NET-EN, due to the inhibition of both ovulation and follicular development. Amenorrhoea may be generally more acceptable to women than prolonged or frequent bleeding.

In one RCT (n=3172), significantly more DMPA users reported amenorrhoea than NET-EN users (12% versus 7% and 24% versus 15% at 1 and 2 years respectively). The prevalence of amenorrhoea increases the longer that POICs are used. No significant differences in the incidence of 'bleeding problems' were reported among DMPA and NET-EN users at 1 and 2 years.[265][EL=1+]

One multinational RCT (n=1216), undertaken mainly in developing countries, compared menstrual diaries in women given DMPA in 100mg and 150mg every three months. The most common bleeding problem for both groups was infrequent bleeding. Amenorrhoea was experienced by 9% -10% of women in the first 3 months and 41% - 47% at 1 year.[269][EL=1-]

In a study which assessed the effect of counselling on compliance in DMPA users, amenorrhoea was the major side effect reported, occurring in 34 to 35% of the women.[69][EL=3]

Summary of evidence

- **Bleeding problems occurred in around 20-40% of DMPA users**

Management of bleeding problems

Amenorrhoea is common in women using DMPA. If unacceptable, an alternative method should be offered.[78][EL=4] Fewer than 10% of women experience prolonged and sometimes heavy bleeding. Underlying gynaecological problems should be excluded if an unexpected change in bleeding patterns occurs.

One RCT (n=278) compared ethinylestradiol, estrone sulphate or a placebo in the treatment of vaginal bleeding (episodes of longer than 7 days) among DMPA users. Treatment success (bleeding stopped for 2 days or more during treatment and not recurred) was significantly higher in the ethinylestradiol group (93% versus 76% versus 74%) than in the other 2 groups. [279][EL=1+]

One RCT in Thailand evaluated the effect of mefenamic acid on controlling irregular uterine bleeding in DMPA users. A significantly higher number of women stopped bleeding in the group given mefenamic acid (n=23; mean BMI 22.3) when compared with the group given placebo (n=25; mean BMI 22.3) in the first week (69.6% vs 40%). However, there was no significant difference in mean bleeding-free days between the two groups at 4 weeks. This suggested that mefenamic acid was not effective in the long-term control of bleeding during DMPA use. [280][EL=1-]

A small RCT in the US evaluated the effect of mifepristone in the prevention of breakthrough bleeding (BTB) in new starters of DMPA. A significant reduction in the number of days of BTB and the number of cycles with prolonged bleeding intervals was reported in women given mifepristone (n=10) when compared with women given placebo (n=10).[281][EL=1-]

In a 6-month cohort study of women who were administered DMPA (n=349) or

NET-EN (n=304) in the puerperium (within 6-12 hours of delivery), no significant differences were identified in the incidence of prolonged (> 21 days) bleeding or in the mean duration of bleeding between groups. In the same study, a subgroup of women was given naproxen or placebo to treat heavy bleeding (n=48). No significant differences were reported between the groups in the duration or amount of bleeding.[282][EL=2-]

(See 3.5)
Three studies have shown that counselling women about bleeding disturbances reduces discontinuation rates in DMPA users. In two 1-year studies (n=350, 421) significantly fewer women who received structured counselling discontinued DMPA use both for all reasons, and for reasons related to bleeding patterns when compared with women who received routine counselling.[69][EL=1+] [283][EL=2+]

A survey in Bolivia (n=352) reported that women advised to return to the clinic if experiencing problems were 2.7 times more likely to continue DMPA at 1 year than those who did not receive such advice. Women advised of the possibility of amenorrhoea were 2.5 times more likely to return for a second injection, whilst those believing regular bleeding to be a requisite for maintaining good health were more likely to discontinue DMPA use.[68][EL=3]

Summary of evidence

- **Ethinylestradiol and mefenamic acid may be effective in the management of bleeding problems associated with DMPA use.**
- **Counselling about bleeding disturbances associated with DMPA use is beneficial in improving continuation rates.**

Recommendations:
Women should be informed that amenorrhoea is a common side effect of injectable contraceptives:

- **it is more likely with DMPA than NET-EN**
- **it is more likely as time goes by**

- **it is not harmful. [C]**

Health professionals should be advised that non-hormonal treatment with mefenamic acid or hormonal treatment with ethinylestradiol may be helpful in managing bleeding problems associated with DMPA use. [D/GPP]

6.5 Common concerns and symptoms

6.5.1 Weight change

Weight fluctuation in women of reproductive age is common, whether or not hormonal contraceptives are used. Weight increases with age in women of child-bearing age and the proportion of those categorised as overweight increases with each age decade. It is estimated that 25% of women in the UK are categorized as obese. [165]. Studies on weight gain during POICs use reported conflicting results. The mechanisms by which contraceptive hormones may affect body weight are not well known.

One multinational RCT reported a mean weight gain of about 3 kg in both DMPA (n=1587) and NET-EN (n=789) users at 2 years.[265][EL=1+]

A systematic review to update the WHOMEC guidance identified 2 studies. A cohort study of adolescent DMPA and COC users (n=239) reported a significantly greater weight gain among overweight DMPA users (~6.2 kg), compared to both 'normal' weight DMPA users (3.1 kg) and overweight OC users (3.4 kg) at 1 year. This was believed to be due to an appetite-stimulating effect and altered tryptophan metabolism. Overweight women may be at increased risk of weight gain. [284][EL=2+]. The other study (n=885) reported similar weight gain (~2 kg) in DMPA users who weighed more or less than 91 kg at baseline.[285][EL=3].

Recommendation:

Women should be advised that DMPA use may be associated with an

increase of 2 to 3 kg in weight over 1 year. [C]

6.5.2 Altered mood

Concerns about the potential for POICs either to cause mood changes or to worsen pre-existing depressive symptoms appear to be unfounded.

A US cohort study reported an increased likelihood of depressive symptoms in DMPA users (n=183) compared with non users (n=274) at 3 years (OR 1.44; 95%CI 1.00 to 2.07), although significantly more DMPA users reported symptoms at baseline (28% versus 18%). Women who discontinued DMPA (62%) also had a greater likelihood of depressive symptoms than non-users (OR 1.60; 95%CI 1.03 to 2.48).[286][EL=2-]

Another US cohort study (n=63) reported no significant differences in mood and depression scores in adolescents (aged 16 to 21) who used DMPA, compared with non-users of hormonal contraception at 1 year.[287][EL=2-]
One US cohort study of adolescents (n=199) reported no differences in depression between users of DMPA and COC (53% versus 57%).[288][EL=2-]

A US cross-sectional survey (n=495) of users of DMPA reported that the 44% continuing to use the method at 1 year had significantly lower baseline scores for depression than did those who discontinued the method or who were lost to follow-up.[289][EL=3]

We did not identify any studies which assessed the effect of POICs on libido.

Recommendation:
Women should be advised that the use of DMPA is not associated with depression. [C]

6.5.3 Acne

Acne is a common skin condition affecting 35 to 90% of adolescents.[290]

Progestogen-only contraceptives, particularly the more androgenic progestogens such as LNG, tend to make the skin greasier and prone to acne.[244] DMPA has relatively low androgenic activity.

A US cross-sectional survey of adolescents users of DMPA (n=35) and Norplant (n=31) reported no difference in the incidence of acne as a reason for discontinuation (9% of DMPA users and 10% of Norplant users).[278][EL=3]

Recommendation:
Women should be advised that the use of DMPA is not associated with acne. [C]

6.5.4 Headache and migraine

Headache is one of the commonest symptoms experienced in the general population, both in young people and in adults. About 70% of adults report headache in the previous 3 months; the prevalence is greater in females than in males.[245] The prevalence of migraine has been estimated to be about 7% among adolescents.[291]

A cohort study (n=199) reported no significant changes from baseline in the occurrence of headaches among COC users or DMPA users at 6 months.[288][EL=2-] The figures for discontinuation due to increased headaches in a small US cross-sectional survey of adolescent users of DMPA and Norplant were similar (26% versus 35%).[278][EL=3]

Recommendation:
Women should be informed that all progestogen-only methods, may be used by women who have migraine with or without aura.
Women should be advised that the use of DMPA is not associated with headaches. [C]

6.6 Risks

6.6.1 Cardiovascular disease

Lipid profiles are considered a surrogate marker for cardiovascular risk. Low HDL-levels and high LDL-levels are independent risk factors for the development of atherosclerosis and cardiovascular disease.

A cohort study (n=42) reported 15% versus 30% decreases in HDL cholesterol from baseline with DMPA versus NET-EN at 1 year.[292][EL=2-] Another cohort study (n=50) reported significantly lower total cholesterol concentrations in Norplant versus DMPA users after 6 months use, with no significant difference between groups in mean HDL cholesterol, LDL cholesterol, or triglyceride concentrations.[293][EL=2-]

One RCT (n=3172) reported mean reductions of 3 and 2.5 mmHg in systolic, and 1.6 to 1.8 mmHg in diastolic, blood pressure in DMPA and NET-EN users at 2 years.[265][EL=1+]

A cohort study in Thailand comparing long-term DMPA users (n=50) with IUD users (n=50) (CuT380A) reported no significant difference in systolic and diastolic blood pressures between the two groups at 120 months.[170][EL=2+]

One case-control study compared women who had used DMPA (n=16) or COC (n=18) for between 18 and 40 months with matched controls using no contraception (n=18). The mean concentrations of fasting plasma total cholesterol, low-density lipoprotein cholesterol (LDL), and apolipoproteins were significantly higher in contraceptive users than in controls, and in COC versus DMPA users.[294][EL=2-]

Unlike the COC, DMPA is not associated with any increase in the risk of stroke, VTE or Myocardial infarction (MI). An international hospital-based case-control study (n=3697 cases, 1% being POICs users; n=9997 controls), assessed cardiovascular disease (CVD) risks among users of progestogen-

only or combined hormonal contraceptives compared with non-users of steroid hormone contraceptives. Current use of POICs did not affect combined CVD risk, or risk of stroke, VTE, or acute MI. The adjusted OR for combined CVD risk in POICs users versus non-users was 1.02 (95% CI 0.68 to 1.54), stroke OR 0.89 (95% CI 0.53 to 1.49), VTE OR 2.19 (95% CI 0.66 to 7.26), and acute MI OR 0.66 (95% CI 0.07 to 6.00).[110][EL=2-]

DMPA and NET-EN are assigned category '3' for women with multiple risk factors for arterial cardiovascular disease, current VTE, ischaemic heart disease or history of stroke. The risks of using POICs may outweigh the benefits.[16]

DMPA is assigned category '4' for women with a blood pressure of over 160/110mmHg.[16]

Recommendation:
Health professionals should know that DMPA, and probably NET-EN, are medically safe for women to use if there is a contraindication to oestrogen. [D/GPP]

6.6.2 Bone mineral density

Concern has been raised about the potential effects of POICs on bone mineral density (BMD) and therefore on fracture risk, particularly among young women who have not yet attained their peak bone mass and among older women, who may be starting to lose bone mass. There is no evidence that POICs cause osteoporosis or fractures.

Several cross-sectional and cohort studies which evaluated the effects of DMPA on BMD, were included in a systematic review conducted for the WHOMEC.[295][EL=2++] Of these studies, few have specifically evaluated the effects of DMPA on BMD in adolescents (two cohort studies and a cross-sectional survey) or in postmenopausal women (one cross-sectional survey). No studies evaluating fracture risk in current or past DMPA

users were found, nor studies evaluating BMD or fracture risk in NET-EN users.

The studies identified are heterogeneous, varying in the age group of women evaluated, in the population and settings, duration of DMPA use, site of BMD measurement, and the method used to measure BMD (three cross-sectional studies used single rather than dual X-ray absorptiometry).[296-298] Some studies compared BMD in DMPA users with users of other methods, including COCs, IUDs, and Norplant. The results are inconsistent, with some studies reporting significantly lower BMD in DMPA users than non-users or users of other contraceptive methods, and others reporting no significant differences.

The results from 8 cross-sectional studies [296;298-304] that measured BMD in current DMPA users (age range 17 to 54 years) were used to derive Z Scores in a review.[305][EL=3] Across these studies, duration of DMPA use ranged from 1 month to at least 5 years, and the number of women evaluated from 100 to 2474. The studies generally reported lower BMD in DMPA users compared with non-users, but all decreases were within 1 standard deviation of the mean of non-users (within a Z score of 1, which does not indicate osteopenia or osteoporosis). The reduction in BMD at sites of predominantly trabecular bone (lumbar spine),[299-301;303;304] femoral neck,[300;301;303;304] ultradistal radius[296;298;302] was greater than at sites of predominantly cortical bone (midshaft ulna).[296;298;302][EL=3]

A 3-year US cohort study of women aged 18 to 39 years reported significant decreases in lumbar spine and proximal femur BMD in DMPA users (n=182) (median duration of use of 11 months) compared with non-users (n=258), about 34% of the latter were taking oral contraceptives, which might increase BMD. In DMPA users who discontinued the contraceptive, BMD increased at both sites.[304;306][EL=2+]

A Swiss cohort study (n=45) of women aged 30 to 45 years, reported a significant reduction in cortical bone mass at the radius in DMPA users versus users of non-hormonal contraceptives, but no significant difference between

groups in changes to trabecular bone mass at 1 year.[307][EL=2+]

A US cross-sectional study in adolescents aged 14 to 18 years (n=174) found no significant differences in BMD of the total body, hip, or lumbar spine between DMPA users (median duration of use 9 months) and non-users.[308][EL=3]

A cohort study assessed BMD changes in adolescents (aged 14-18 years) using and discontinuing use of DMPA. It reported a significant decline in BMD at the hip and spine among DMPA users (n=80) compared with non-users (n=90). There was no significant difference in BMD changes for the whole body between the two groups. Of the adolescent DMPA users, 61 (71%) discontinued at some point during the 3-year follow-up, and 21% discontinued within the first 6 months of enrolment. Discontinuers experienced significantly increased BMD relative to non-users at all anatomical sites. This post-continuation gains in BMD suggested that the loss of bone mass may be reversible.[309][EL=2]

In additional to the above studies, a cross-sectional study of adolescents (n=174) aged 14 to 18 years reported no significant differences in BMD of the total body, hip, or lumbar spine between DMPA users (median duration of use 9 months) and non-users.[308][EL=3]

A cohort study of adolescents aged 11 to 21 reported a significant decrease in BMD in DMPA users (n=58) versus COC users (n=71) at 12 and 18 (but not at 6 and 24) months.[310][EL=2-]

One cohort study (n=370) assessed the relationship between biochemical markers of bone metabolism and DMPA, COC use or non-users among adolescent girls aged 12-18. It reported evidence of increased bone formation and resorption in those who used no hormonal contraception when compared to those in the DMPA and COC group at 12 months, suggesting possible suppression of bone metabolism in the DMPA and COC groups. [311][EL=2-]

A cohort study (n=496) assessed BMD in DMPA users aged 40-49 and reported no significant difference in BMD between users of DMPA, NET-EN, COC and non-user controls. Long-term use of DMPA does not negatively impact on BMD in women aged 40-49, suggesting that women can continue using this method till menopause. [312][EL=2+]

A cohort study in New Zealand compared the rate of menopausal bone loss in long-term users of DMPA until reaching menopause (n=16) with a control group of women who did not previously use DMPA and reached a natural menopause (n=15). It reported rapid menopausal bone loss from the lumbar spine and femoral neck in the control group (6% from both sites over 3 years), and DMPA users showed little change in BMD.[313][EL=2-]

Among postmenopausal women who were past users of DMPA (n=34) compared with non-users (n=312), no significant differences in BMD of the total body, lumbar spine or femur were reported in one survey. The median duration of past DMPA use was 3 years (range 0.2 to 18.1).[314][EL=3]

Four cross-sectional studies reported BMD results in women who had used DMPA or a COC for at least 2 years.[296;297;315;316] Whilst one study reported that BMD at the distal radius was significantly lower in DMPA versus COC users (n=2474),[296] the other 3 studies did not report significant differences in BMD at the forearm, lumbar spine, or femur (n=60, 155, 189).[297;315;316][EL=3] Three cohort studies also reported BMD in DMPA versus COC users, two of which were conducted in adolescents (age range 12 to 21 years). One of the adolescent studies reported significantly lower BMD in DMPA users versus COC users at 12 and 18 (but not 6 and 24) months.[310][EL=2-] The other reported that BMD decreased in users of DMPA compared with increases in COC or Norplant users, although absolute BMD values were not significantly different among groups at 1 year.[317][EL=2-] A US cohort study (n=346) in new users of hormonal contraception (aged 18 to 33 years) reported significantly greater loss of lumbar spine BMD in DMPA users compared with users of COCs or non-hormonal methods at 12 months.[318][EL=2+] In a follow-up study, the effect of DMPA use on BMD at 24 months was reported to be linear, with

a total mean BMD loss of 5.7% (3.2% loss between months 12 and 24) in DMPA users vs 2.6% among pill users. [319][EL=2+] Another cohort study (n=323) reported a similar linear pattern in BMD loss among DMPA users (2.8% at 12 months, accumulating to 5.7% at 24 months). Among DMPA users, BMI change was inversely associated with BMD change at the hip, but not the spine. [320][EL=2+]

A 6-month cohort study (n=19), comparing BMD of the forearm, and biochemical and urinary markers of bone metabolism in DMPA and Norplant users, did not identify significant differences between groups in any of these parameters.[321][EL=2-]

A cross-sectional survey in women who had used DMPA or an IUD for at least 3 years (n=100) reported no differences between groups in forearm BMD.[302][EL=3]

A small UK general practice cross-sectional study measured lumbar spine and femoral neck BMD scores in DMPA users with low oestrogen levels or displaying menopausal symptoms (n=32). T and Z scores were below the mean at both sites. Mean duration of DMPA use was 52 months.[322][EL=3]

Summary of evidence

- **There is conflicting evidence that DMPA reduces bone mineral density which may be reversible on discontinuation.**

Management of oestrogen deficiency induced by DMPA

A double-blind RCT examined the effects of oestrogen (n=19) versus placebo (n=19) on BMD in long-term DMPA users who had below average baseline spinal BMD. It reported a significant difference in changes in spinal BMD (a mean increase of 1% in among DMPA users who received oestrogen replacement therapy versus a drop of 2.6% in the placebo group) at 2 years. The between group differences were significant at 18 months and 24 months respectively (3.2% versus 3.5%).[323][EL=1+]

Another double-blind RCT assessed the effect of oestrogen supplementation on BMD in adolescent girls who received DMPA for contraception. It reported significant higher BMD in the group given estradiol cypionate (n=65) when compared with that in the group given placebo (n=58) at 24 months (drop-out rate 53%). Oestrogen supplementation may be protective of bone in adolescent users of DMPA.[324][EL=1-]

The Department of Health issued an alert in November 2004 on the use of DMPA.[325] The advice is that DMPA should be used as a first-line contraceptive in adolescents only after other methods have been discussed with the individual and considered to be unsuitable or unacceptable. Women of all ages should have the method re-evaluated after 2 years' continuous use. Women with risk factors for osteoporosis should consider other methods. The FFPRHC also issued guidance on the use of DMPA in relation to BMD. [326]

Summary of evidence

- **Oestrogen supplementation may be effective in the management of bone mineral density reduction in DMPA users.**

Recommendations:

All women should be advised that the use of DMPA is associated with a small loss of bone mineral density, which may be recovered when the method is discontinued. [B]

There is no evidence that the use of DMPA increases the risk of fracture. [B]

All women who wish to continue DMPA beyond 2 years should have their individual clinical situation reviewed and be supported in their choice. Their continued use of the method should be reviewed at regular intervals. [D/GPP]

Care should be taken in recommending DMPA to adolescents but DMPA may be given if other options are not suitable or acceptable. Their individual clinical situation should be reviewed at regular intervals. [D/GPP]

Osteoporosis

We did not identify any studies which addressed this question.

Research recommendation:

- Research on the effectiveness, discontinuation, bleeding patterns and bone mineral density in women in the UK who have used DMPA for longer than 2 years.

6.6.3 Ectopic pregnancy

We did not identify any studies which addressed this question.

6.6.4 Women who become pregnant while using DMPA

The WHOMEC states that if a woman using a POIC is found to be pregnant, there is no known harm to the woman, the course of her pregnancy or the fetus. However, the relationship between DMPA use during pregnancy and its effects on the fetus remains unclear.[16][EL=4]

Recommendation:

If pregnancy occurs during the use of DMPA there is no evidence of harm to the fetus. [D/GPP]

6.7 Return to fertility

POICs are the only progestogen-only method to cause a delay in the return of fertility. The delay for DMPA is greater than for NET-EN.

Seven non-comparative studies reported that ovulation occurred between 3 to 6 months after DMPA injection. [327;327-332][EL=3]

One cohort study (n=24) reported significant differences in the time it took for ovulation to return among DMPA and NET-EN users 90 days after their last injection (5.5 versus 2.6 months).[333][EL=2-]

A cohort study reported median delay before conception of 5.5 months in DMPA users (n=796) versus 4.5 months in IUD users (n=125) after removal. Cumulative conception rates in both groups were not significantly different (78% and 92% of DMPA users versus 79% and 93% of IUD at 1 and 2 years respectively).[334][EL=2-]

A cohort study (n=98) reported no significant difference in cumulative pregnancy rates following discontinuation of Norplant or DMPA (76% versus 70%; RR1.09, 95% CI 0.86 to 1.39 at 1 year and 90% versus 89%; RR 1.01, 95% CI 0.88 to 1.15 at 2 years respectively).[335][EL=2+]

A questionnaire survey of pregnant women in the UK reported mean times to pregnancy (TTP) of 2.0, 2.2 and 3.9 times longer after the discontinuation of COC (n=925), IUD (n=82) and injectable (n=62) respectively when compared with condom use (n=389). Conception rates within 6 months of discontinuation were 71%,77%, 27% and 25% among users of COC, IUDs, injectable and implants (n=4) respectively, compared to 82% among condom users. Relative to condoms, the odds of subfecundity were 1.9, 5.5 and 2.9 respectively among users of COC, injectable and short-term IUD. The effect of injectables was stronger with long-term use in older, obese or oligoamenorrhoeic women. [207][EL=3] (see 4.8.2, 5.8 and 7.7.2)

Recommendations:

Women should be informed that there could be a delay of up to 1 year in the return of fertility after discontinuation of injectable contraceptives. [C]

Women stopping injectable contraceptives but not wishing to conceive should be advised to use a different method of contraception immediately. [D/GPP]

6.8 Details of method use

6.8.1 Assessment prior to initiation

(See 3.6 for recommendation)

The UKSPR recommends that blood pressure screening is desirable before initiation of POICs. [78][EL=1-4]

6.8.2 Site of injection

Both injections are given by the deep intramuscular route, preferably into the gluteal region. They may be given into the deltoid in obese women where it is thought that the needle will not reach muscle.

Recommendation:
The gluteal, lateral thigh and deltoid are all acceptable sites for injectable contraceptives. [D/GPP]

6.8.3 Information prior to injection

(See 3.5)

Recommendation:
Women should be advised of failure rates, benefits, risks and side effects of injectable contraceptives. [D/GPP]

6.8.4 Time of first Injection

In a normal menstrual cycle

The UKSPR (adapted from the WHOSPR and based on evidence and consensus) recommend that progestogen-only injectables can be started up

to and including the 5th day of the menstrual cycle. No additional contraceptive protection is needed. Injection can be given at any other time in the cycle if reasonably sure that the woman is not pregnant. Either the woman will need to abstain from sex or additional contraceptive protection should be used for the first seven days after injection.[78][EL=4]

One non-comparative study (n=150) examined the level of pregnancy risk and the bridge preferences of women requesting DMPA who were ineligible for initial injection due to the menstrual cycle day. It reported that 98% of the women rejected the standard protocol of waiting with condoms or abstinence in favour of a hormonal bridge method (oral contraceptives with the directly observed ingestion of the first pill in the clinic; or a monthly combination injection of DMPA 25 mg and estradiol cyprionate 5mg immediately) and return to the clinic at a scheduled time to initiate DMPA. Eighty-six percent were satisfied with the bridge method. Women reporting unprotected intercourse within 120 hours before their visit received emergency contraception administered in the clinic.There were no post-treatment pregnancies.[336][EL=3]

Recommendation:
Injectable contraceptives may be started up to and including the fifth day of the menstrual cycle. No additional contraceptive protection is needed. Injectable contraceptives may be given at any other time in the cycle if it is reasonably certain that the woman is not pregnant; additional contraception should be used for the first 7 days after injection. [D/GPP]

Management of delayed injections
(See also 6.7)

For delayed injections, the UKSPR recommended that repeat injections may be given up to 2 weeks late without additional contraceptive protection.[78][EL=4] If given beyond this time, additional protection is required for 7 days.

The UK Electronic Medicines Compendium (*e*MC) recommends that if the interval from the preceding DMPA injection is greater than 89 days (12 weeks and 5 days) for any reason, women should be advised to use additonal contraceptive measures for 14 days after this subsequent injection.[337]

Recommendations:
Repeat injections of DMPA should be given every 12 weeks and for NET-EN every 8 weeks. [C]

Women attending up to 2 weeks late may be given DMPA or NET-EN injection without the need for additional contraceptives if it is reasonably sure that they are not pregnant. [D/GPP]

Following termination of pregnancy

We did not identify any studies reporting on the use of DMPA following induced abortion.

One cohort study (n=10) reported on ovulation in women given NET-EN or an IUD on the day of first trimester abortion. No ovulations occurred within 8 weeks of NET-EN administration. Ovulation occurred in each of the IUD users after day 25.[338][EL=2-]

A systematic review to update the WHOMEC has extrapolated evidence from studies conducted with other progestogen-only methods to provide a rationale for the use of POICs post-abortion. There is no known clinical thrombogenic effect of progestogen-only contraceptives; therefore POICs can be safely used immediately post-abortion (spontaneous or induced).[261][EL=4]

DMPA and NET-EN are assigned category ‘1’ for women immediately after abortion in the current WHOMEC recommendations.[16][EL=1-4]

The RCOG guideline on Abortion recommended that any chosen method of contraception should be initiated immediately after abortion. [213][EL=1-4]

Post delivery

The UKSPR recommends that the first injection of DMPA can be given at any time between 6 weeks and 6 month post-partum if the woman is amenorrhoeic.[78][EL=1-4]

Recommendations:
DMPA and NET-EN may be given immediately following abortion in any trimester (spontaneous or induced). [D/GPP]

DMPA and NET-EN may be initiated at any time post partum if it is reasonably certain the woman is not pregnant.[D/GPP]

6.9 Training of health professionals

(See 3.14)

6.10 Specific groups

Adolescents

(See 6.6.2 for recommendation)

Women aged over 40 years

(See 6.6.2)

The use of POICs by women older than 40 years needs caution.[339][EL=2-] It is important to evaluate irregular bleeding before administering POICs, and to consider endometrial abnormalities as a possible cause if the woman returns with irregular bleeding after prolonged amenorrhoea. The inevitable loss of BMD following the menopause may be exacerbated if POICs are used during the perimenopause.

POICs are assigned category '2' for women over 45 years of age in the current WHOMEC recommendation.[16].

Recommendation:
Care should be taken in recommending DMPA to women aged over 40 because of the possible effect on bone mineral density but in general the benefits outweigh the risks. [D/GPP]

Women with body mass index over 30

We did not identify any studies which assessed the relationship between body weight and efficacy of POICs.

A systematic review to update the WHOMEC reported no significant differences in the incidence of increased or excessive bleeding between obese (BMI over 30 kg/m^2), overweight (BMI 25 to 29.9 kg/m2), and non-obese (BMI under 25kg/m2) DMPA users of at least 9 months.[16;285][EL=2++]

Recommendation:
Women with a body mass index over 30 can safely use DMPA and NET-EN. [D/GPP]

Women who are breastfeeding

Concern has been expressed that progestogens may affect breast milk constituents and hence the baby.

A cohort study in women recruited 6 weeks after childbirth (n=140) reported that mean milk concentrations of calcium, phosphorus, sodium, potassium, and protein were similar at 26 weeks postpartum in users of POICs (oral or DMPA, n=51) and non-hormonal contraception (n=89). Triglyceride levels were significantly higher in the women using progestogen-only methods, and magnesium levels significantly higher in the women using non-hormonal methods.[340][EL=2-]

Two US cohort studies investigated the impact of DMPA on breastfeeding in postpartum women. One (n=319) reported no significant differences between groups in the proportion of women who continued to breast-feed, supplemented breastfeeding with bottle-feeding, or who discontinued breast-feeding within 6 weeks postpartum due to insufficient milk.[341][EL=2+] Another cohort study (n=95) reported no differences between users of DMPA or non-hormonal contraception in the duration of breastfeeding or in the timing of the first introduction of formula feed during the first 16 weeks postpartum.[342][EL=2+]

DMPA and NET-EN are assigned category '3' for women during the first 6 weeks post-partum and who are breastfeeding in the current WHOMEC recommendations.[16][EL=1-4] The UKSPR states that for women who are less than 6 weeks postpartum and primarily breast feeding, POICs are not usually recommended unless other methods are not available or are unacceptable.[78]

DMPA and NET-EN are assigned category '1' for women who are 6 weeks or over 6 weeks post-partum and breastfeeding in the current WHOMEC recommendations.[16][EL=1-4]

Recommendation:
Breastfeeding women may be advised that they can use injectable contraceptives imediately after childbirth if other methods are unacceptable. [D/GPP]

6.11 Medical conditions and contraindications

Diabetes

We did not identify any studies which addressed the effect of POICs use in people with diabetes.

Epilepsy

In a case-series study, MPA (oral in 8 women, DMPA in 6) was added to the antiepileptic drug regimen of those who had uncontrolled seizures. Significant reductions in mean monthly seizure frequency of 39% were reported from baseline.[343][EL=3]

DMPA and NET-EN are assigned category '1' for women with epilepsy in the current WHOMEC recommendations.[16][EL=1-4]

Recommendations:

Women should be informed that progestogen-only injectable contraceptives are not contraindicated for women with diabetes. [D/GPP]

The use of DMPA may be associated with a reduction in the frequency of seizures in women with epilepsy requiring contraception. [D/GPP]

Sexually transmitted infections, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)

(See 3.11)

A systematic review to update the WHOMEC reported limited evidence that there may be an increased risk of chlamydial cervicitis, a lower genital tract infection, among DMPA users at high risk of STIs. Evidence for risks of other STIs is insufficient and inconclusive.[16;217][EL=1-4]

The use of hormonal contraceptives by HIV-1-seronegative women has been associated with an increased risk of the acquisition of cervical STI, including chlamydial infection, gonorrhea and non-specific cervicitis.[344-346]

A 10-year cohort study (n=242) in Kenya evaluated the relationship between hormonal contraceptive use and the acquisition of STI among HIV-infected women. It reported a significant increased incidence of cervical chlamydial

infection (Hazard ratio 3.1, 95% CI 1.2 to 8.4) and cervicitis (Hazard ratio 1.6, 95% CI 1.1 to 2.4) in DMPA users (n=79) when compared with women who used no contraceptive method (n=124). OC users (n=37) had a significantly increased incidence of cervicitis (Hazard ratio2.3, 95% CI 1.4 to 3.6).[347;348][EL=2-]

A systematic review to update the WHOMEC reported inconsistent evidence regarding the increased risk of HIV acquisition among users of progestogen-only contraceptive compared with non-users. There is conflicting evidence whether there is an increased risk of HIV and herpes simplex virus (HSV) shedding among HIV-infected women using DMPA.[16;217][EL=1-4]

Recommendation:

There is no evidence to suggest a causal relationship between the use of DMPA and an increased risk of STI or HIV acquisition. Women at increased risk of STI, including HIV/AIDS, may use DMPA and NET-EN. POICs do not protect against STI/HIV and if there is a risk, the correct and consistent use of condoms in addition to the injectable contraceptives is recommended. [D/GPP]

6.12 Drug interactions

The UK Summary of Product Characteristics for DMPA states that “the clearance of medroxyprogesterone acetate is approximately equal to the rate of hepatic blood flow. Because of this fact it is unlikely that drugs which induce hepatic enzymes will significantly affect the kinetics of medroxyprogesterone acetate. Therefore no dosage adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.”

The Summary of Product Characteristics for NET-EN states that “Some drugs may accelerate the metabolism of Noristerat. Drugs suspected of having this capacity, which may reduce the efficacy of the preparation, include barbiturates, carbamazepine, phenytoin, phenylbutazone, griseofulvin and

rifampicin. The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance."

Recommendation:
It is not considered necessary to avoid the use of injectable contraceptives in women taking liver enzyme-inducing medication or to reduce the injection interval. [D/GPP]

6.13 Follow-up

We did not identify any studies which addressed follow-up care in women using DMPA or NET-EN.

Repeat DMPA injections should be provided every 12 weeks, and repeat NET-EN injection every 8 weeks.

In a 1-year RCT (n=250), sending reminders of their next injection to women did not reduce the number of missed appointments compared with those not sent a reminder (39% versus 33%, RR 1.16, 95% CI 0.83 to 1.62). Continuation rates were not significantly different between groups (43% versus 45%, relative risk 0.94, 95% CI 0.71 to 1.25).[349][EL=1+]

Recommendation:
A repeat follow-up visit is required every 12 weeks for DMPA users and 8 weeks for NET-EN users. [D/GPP]

6.14 Economic evidence

According to the results of the economic evaluation of LARC methods undertaken for this guideline, the injectable dominates the male condom and COC across all time horizons considered. This means that the injectable is associated with both lower numbers of unintended pregnancies and lower costs compared to the male condom and COC.

Over all, the injectable is less effective than male and female sterilisation due to high discontinuation rates (associated with all LARC methods). It is also less costly for short periods of use. Male and female sterilisation become dominant over injectable (that is they become both more effective and less costly) at 3 and 5 years of contraceptive use respectively and above.

The injectable is dominated (i.e. it prevents a lower number of pregnancies overall and incurs higher total costs) by all other LARC methods, i.e. IUS, the implant and IUD, for periods of use starting from 2 and up to 15 years. For one year of use, the injectable is the cheapest but also the least effective among LARC methods; the Incremental Cost Effectiveness Ratios (ICERs) of the IUS, the implant and the IUD, compared to the injectable for one year of use are £5,100, £4,141, and £339 per pregnancy averted respectively.

Evidence statement

- **The injectable is more cost-effective than the male condom and COC, even for short periods of contraceptive use, starting at one year.**

- **Male and female sterilisation are more cost-effective than the injectable for periods of use starting from 3 and 5 years respectively.**

- **The injectable is less cost-effective than any other LARC method for periods of contraceptive use equal to 2 years and above.**

Full results of the economic analysis are presented in Chapter 8.

7. Progestogen-only subdermal implants (POSDIs)

7.1 Introduction

7.1.1 What they are

Contraceptive implants are inserted subdermally under the skin in the upper arm. Implanon is currently the only subdermal implant licensed for use in the UK. Norplant has not been marketed in the UK since 1999. However, it is still in use in many other countries and women still attend UK clinics requesting removal. Jadelle® (Norplant-2) has not been marketed in the UK, but is licensed elsewhere in the world and women sometimes attend UK clinics requesting removal.

7.1.2 Mechanism of action

Implanon is a single-rod contraceptive implant (40mm x 2mm) which contains 68 mg of etonogestrel (ENG) dispersed in a membrane of ethylene vinyl acetate. Implanon delivers ENG at a dose sufficient to suppress ovulation in every cycle throughout the 3 years of use.[350;351]

Norplant consists of six flexible, sealed capsules (34 mm x 2.4 mm), each containing 36 mg of levonorgestrel (LNG). Norplant-2 (Jadelle) consists of 2 rods containing a total of 150 mg of LNG. Norplant and Jadelle prevent normal sperm transport by altering the characteristics of cervical mucus and also preventing normal development of the endometrium.[350] The dose of LNG delivered with time falls significantly. In the first year of use fewer than 10% of cycles are ovulatory. By the fifth year ovulation occurs in more than 50% of cycles.[352;353]

Recommendation:
Women should be advised that implants work by altering the endometrium and cervical mucus and in a proportion by preventing ovulation. [C]

7.1.3 Use in the UK

It is estimated that fewer than 3% of women aged 16-49 in Great Britain chose implants as their method of contraception in 2003/04.[1][EL=3].

7.1.4 Duration of action

Implanon is licensed for 3 years. Norplant and Jadelle are both licensed for 5 years.

Recommendation:
Women should be informed that Implanon lasts for 3 years. [C]

7.1.5 The evidence

A systematic review designed to assess relative effectiveness, acceptability, tolerability and cost-effectiveness of Norplant, Jadelle and Implanon was undertaken by the NHS Health Technology Assessment (HTA) Programme in the late 1990s.[125] For subdermal contraceptive implants, 34 comparative studies met the inclusion criteria for the review including 15 RCTs and 19 non-randomised prospective cohort studies.

The majority of the studies (59%) were undertaken in developing countries and 12% were multicentre studies which included sites in developing countries. The RCTs included a total of 1771 women from developing countries and 656 women from developed countries. The cohort studies recruited 5045 women from developing countries and 459 women from developed countries.

The Guideline Development Group (GDG) has reservations about the relevance of many of these studies to the UK population. For example, the group felt it inappropriate to use data on continuation rates from countries where access to contraception is limited and/or expensive. Similarly, data from countries where women are characteristically of significant lower body weight (such as Indonesia or Thailand) than women in the UK, may overestimate the effectiveness of hormonal methods of contraception and the incidence of ameorrhoea. (See 3.4 and 3.10) Additionally, some of the studies used to compare the effectiveness of implants with other methods included in the HTA review were limited to specific subgroups, such as adolescents or breastfeeding women. The GDG did not feel it appropriate to use data from these studies in considering women of reproductive age in the general population in UK.

Available data on the effectiveness and efficacy of Implanon are presently limited to a number of clinical trials conducted by the manufacturer comparing Implanon and Norplant in multicentre studies between 1989 to 1998 (2423 women, 75,050 cycles in the Implanon group versus 819 women, 28,109 cycles in the Norplant group). Data from these clinical trials (a total of 8 RCTs and 12 non-comparative studies) formed one integrated database and have been analysed by one systematic review[125] and a series of meta-analyses[354-359]. Reports from individual trials from the same series have also been published by different authors.[54;360-364]

We received information in July 2004 from this pharmaceutical company that, as a result of protocol violation, data from 5 trials (3 RCTs and 2 non-comparative studies) carried out in Indonesia were to be excluded retrospectively. A revised analysis, including data from new trials, was expected in November 2004. However, no revised analysis was available and evidence from one non-comparative study [54] to represent the clinical efficacy of Implanon was resubmitted.

A press report issued by the Dutch Medicines Evaluation Board at the Hague in October 2004 stated that Implanon is ‘still considered to be

effective and safe, provided it is inserted in the appropriate manner according to the product information.'[365] Evidence which compared Implanon with Norplant presented in this chapter is based on original published data from these clinical trials and may contain data from Indonesia before the Indonesian trials were withdrawn, and should therefore be interpreted accordingly. References to these trials are marked with an asterix (*).

Where no studies comparing the use of Implanon with other methods of contraception were identified, indirect evidence from Norplant studies was reviewed (and extrapolation made). The GDG is aware that Implanon and Norplant differ in many respects. They contain different progestogens; the duration of action differs and the number of implants differs. Importantly, in terms of both efficacy and side effects, Implanon inhibits ovulation in almost all women for three years while the number of ovulatory cycles increases with time among Norplant users. By 5 years, over 50% of Norplant cycles are ovulatory. The presence or absence of ovulation significantly affects bleeding patterns and thereby side effects. In the absence of long-term data on Implanon, and where the GDG felt that it was reasonable to do so, data on Norplant has been included. Since Implanon is licensed for 3 years and Norplant for 5 years, wherever possible data from Norplant use at 3 years have been used. Data on Norplant, particularly on efficacy, come largely from trials sponsored and/or organised by the developer (a not-for-profit organisation).

7.2 Effectiveness

Implanon versus Norplant

Two meta-analyses of clinical trials (8 RCTs and 12 cohort studies; n=2043 women, 74,000 cycles) reported no pregnancies and no ectopic pregnancies in women using either Implanon or Norplant at 3 years.[355*354*][EL=1-]

A NICE technology appraisal (n= 7 RCTs; 1628 women; 43001 woman months of follow-up) reported no pregnancies at 4 years among women using

Implanon or Norplant.[125]*[EL = 1-] The RCTs reviewed were part of the multinational clinical trials conducted by a pharmaceutical company.[354]*

A cohort study in China compared the use of Implanon (n=75) and Norplant (n=25) reported no pregnancy in both groups at 4 years. [366][EI=2-]

Implanon

A non-comparative study (n=60) in Spain reported no pregnancies among Implanon users at 1 year. [367][EL=3]

A retrospective chart review (n=132) of Implanon users in the UK reported no known pregnancy at 3 years (15% of women were lost to follow-up). [368][EL=3]

Norplant versus other contraceptive methods

A 5 year multicentre controlled cohort study (n=16,021), undertaken mainly in developing countries, assessed the effectiveness and safety of Norplant (n=7977), compared to women using IUDs (n = 6625) and sterilisation (n=1419). A five-year follow-up was completed by 94.6% of the women enrolled. The cumulative pregnancy rates for Norplant, copper IUDs and sterilisation were 0.12, 1.02, 0.21 and 0.53, 3.04, 0.5 respectively at 1 and 3 years.[174;369][EL=2+]

A cohort study which compared Norplant (n=36) and Nova-T IUD (copper surface 200)(n=23) reported no pregnancy in either group at 1 year.[370][EL=2-]

Another cohort study reported no pregnancies among Norplant users (n=200), compared with a pregnancy rate of 33% among condom users (n=99) and 30% among COC users (n=100) at 2 years.[55][EL=2+]

The GDG considered this evidence, but was aware that pregnancies have been reported during Implanon use. Contraceptive failure may occur for a number of reasons including incorrect implant insertion; pregnancy established at the time of implant insertion; drug interactions and method

failure. No data are available on the cause of pregnancies that have been reported to occur during Implanon use.

Spontaneous reports to the Medicines and Healthcare Products Regulatory Agency (MHRA) (through the Yellow Card Scheme) of suspected adverse drug reactions relating to Implanon included 115 unintended pregnancies from 1999 to 2005. (NB This does not necessarily mean that use of Implanon caused the reaction.)[371]

MDA National, a medical indemnity insurer in Australia, quoted that about 100 pregnancies have been reported in Australia in the first 18 months of use of Implanon. (Unpublished data submitted to MDA National (http://www.mdanational.com.au/default.asp] from Organon Australia)[372]

Summary of Evidence

- **No pregnancies were reported in clinical studies in women using Implanon.**
- **From the clinical experience of the GDG and from post-marketing surveillance, there were reports of pregnancies using Implanon.**

Recommendation:

Women should be advised that subdermal implants, including Implanon, have very low pregnancy rates (less than 0.1 in 100 over 3 years). [C]

7.3 Discontinuation and reasons for discontinuation

(See 3.10)

Most methods of contraception can be discontinued without the involvement of a health professional. However, to stop using an implant, a woman does need to visit a health service facility. In the UK, a relatively small number of health professionals have been trained to remove implants. The geographical inconvenience of attending a particular clinic for implant removal may mean women have to postpone removal for longer.[373] In many countries

the cost to the individual of the implant and implant insertion and the additional cost of both removal of the implant(s) and provision of a new method may encourage longer continuation than that typical of the UK. Evidence on continuation rates for Norplant beyond 3 years of use was ignored by the GDG since Implanon is only licensed for 3 years.

Implanon versus Norplant

The overall discontinuation rate was reported to be 18% at 2- 3 years. The major reasons for discontinuation were bleeding irregularities (but not amenorrhoea)and adverse effects. [355]* Discontinuation rates due to amenorrhoea and bleeding irregularities between Implanon and Norplant users in the European RCTs were 30.2% versus 22.5% (1.6% versus 3.1% for amenorrhoea; 15.5% versus 13.2% for frequent irregular bleeding ; 0.8% versus 2.3% for menorrhagia, 7.8% versus 3.9% for prolonged menstrual flow and 4.7% versus 0.0% for spotting). Three meta-analyses of clinical trials reported adverse events other than bleeding irregularities as the primary reason for discontinuation in 6% of Implanon users versus 7.6% of Norplant users at 2 years.[355*358*354*][EL=1- to 3]

Data from one non-comparative study (n=635, part of the multicentred clinical trial) reported a discontinuation rate of 20% and 31% at 2 and 3 years. Discontinuation rates due to bleeding irregularities were 17% and amenorrhoea 1.7%. [54][EL=3]

Interim data from an unpublished study in Edinburgh (n=329 Implanon insertions; data completed on 262 women) reported a removal rate of 11% within 6 months, 25% at 1 year, 44% at 2 years and 55% at 2 years 9 months respectively. At the end of 3 years, 34% requested a new implant. Discontinuation due to planned pregnancy was 10% and 8% discontinued because the women had no partners. The most frequent reported reason for discontinuation to date was bleeding (32% due to amenorrhoea or frequent bleeding episodes) [374][EL=3]

Implanon

A multicentre non-comparative study (n=1183) in Switzerland reported the premature removal of Implanon in 24% of users, 20% of which were due to side-effects. Side-effects leading to discontinuation were mainly bleeding disturbances (45%), acne (12%), weight gain (7%), depressive moods (5%) and insertion site problems (3%) among Implanon users at 1 year. [375][EL=3]

A non-comparative study (n=60) in Spain reported discontinuation rate of 11.7% due to bleeding disturbances at 1 year. [367][EL=3]

A retrospective chart review (n=132) in the UK reported removal rate of 17% among Implanon users at 3 years. The primary reasons for Implanon removal were abnormal bleeding (12%) and severe mood changes (9%). Using the Kaplan-Meier method, this study calculated the assumed lifetimes of Implanon to be 0.90 (9%% CI 0.82 to 0.95) at 1 year, 0.80 (95% CI 0.67 to 0.88) at 2 years and 0.75 (95% CI 0.58 to 0.85) at 35 months. Older women are less likely to have an implant removed for all side-effects (Hazard ratio 0.9; 95% CI 0.81 to 0.99). [368][EL=3]

A non-comparative study (n=108) in France reported removal rate of 27% at 20 months among Implanon users. The reasons for discontinuation included menorrhagia (41%), amenorhoea (21%), weight gain (21%), acne (14%), headaches (10%) and loss of libido (3%). In this study, the average durarion of Implanon use was 16 months. [376][EL=3]

Norplant versus other contraceptive methods

A 5 year multicentre controlled cohort study (n=16,021 women), undertaken mainly in developing countries, reported a significant difference in the cumulative discontinuation rate of 20.9% and 21.2% for Norplant and copper IUD (a combination of TCu 220C, TCu 380A, Multiload 250 and 375 or Shanghai V) respectively at 3 years. The cumulative discontinuation rates ranged between 4.6% to 21% versus 7.2% to 21.2% in the first 3 years. Excessive bleeding was the most frequent medical reason for discontinuation

among Norplant users, at 9.4% versus 4.7% in the copper IUD group at 3 years.[174;369][EL=2+]

A cohort study (n=755) compared discontinuation rates between Norplant and IUD users in Edinburgh. The discontinuation rates reported were significantly different between Norplant users and IUD users (16% versus 30% and 28% versus 43% at 1 and 2 years respectively). Bleeding problems (menstrual irregularity for Norplant users and menorrhagia for IUD users) were the main reason given for 45% and 38% of Norplant and IUD removals respectively. Removal due to menorrhagia-related pain was reported in 4% of Norplant users and 15% of IUD users. Other reasons for removal included mood swings (39% versus 0%), weight gain (16% versus 0%), headaches (13% versus 0%) and acne (7% versus 0%) in Norplant and IUD users respectively.[373][EL=2+]

A cohort study reported cumulative discontinuation rates for any reason of 18% and 36% among Norplant users (n=200) versus 60% and 64% in COC users (n=100) versus 48% and 58% in condom users at 1 and 2 years respectively.[55][EL=2+]

Summary of Evidence

Table 7.1 Discontinuation rates %: Implanon

Study	**Discontinuation rates %**			
		Implanon	**Rate measured at point (year)**	**EL**
	Overall			
[355]		18	2-3	3
[54]		20	2	3
		31	3	
[374]		25	1	3
		44	2	
		55	3	
[375]		24	1	3
[368]		17	3	3
[376]		27	2	3

- **The commonest reason for discontinuation of contraceptive implants is bleeding disturbances.**
- **Almost one third of women will have had an implant removed within two years because of bleeding problems.**
- **Six percent of women will discontinue Implanon within two years for reasons other than bleeding disturbance, including reasons attributable to hormonal changes.**

Recommendation:
Women should be aware that up to 33% of women will discontinue Implanon within 3 years because of irregular bleeding. Fewer than one in ten women will discontinue for other reasons including hormonal effects. [C]

7.4 Adverse effects

A systematic review to update the current WHOMEC recommendations reported no serious adverse effects among healthy Implanon users.[377] [EL=1-3] Implanon and Norplant are assigned a category '1' rating for healthy women from menarche to before the menopause (18 to >40).[16] [EL=1-4]

A meta-analysis of clinical trials reported no death in any of the clinical development trials of Implanon.[354*] [EL=3] A 5 year multicentre controlled cohort study (n=16,021 women), undertaken mainly in developing countries, comparing the effectiveness and safety of Norplant, IUDs, COC and sterilisation reported 34 deaths, of which 11 were in Norplant users. Five deaths were related to accidents, two suicides, one as a result of lymphoma and one from stroke. The remaining two deaths were related to the reproductive system: one as a result of septic abortion one year after Norplant removal; another death occurred in a woman with a clinical diagnosis of metastastic breast cancer.[112;174] [EL=2+] None of these deaths was

considered to be a direct consequence of the contraceptive implant.

Implanon

A non-comparative study (n=108) in France reported that, of the 81% of women who were satisfied with the use of Implanon, adverse effects occurred in 47% of women.[376][EL=3]

Summary of Evidence

- **In the absence of long term data on Implanon the GDG considered it appropriate to extrapolate from Norplant data.**
- **Implanon use is not associated with serious adverse effects.**

7.4.1 Bleeding problems

Bleeding patterns experienced by women using progestogen-only contraceptive methods include regular bleeding episodes, amenorrhoea, dysmenorrhoea, infrequent bleeding, frequent bleeding, prolonged and heavy bleeding .

Disturbances of menstrual bleeding are common among women who are not using contraception. The prevalence of dysmenorrhoea in the general population is estimated to be about 72% in young women.[378] In untreated women of reproductive age, amenorrhoea occurs in about 1% of women aged 30. The figures for infrequent bleeding and prolonged bleeding are about 8% and < 0.1% respectively.[379]

Implanon versus Norplant

One meta-analysis of clinical trials reported a significant difference in the occurrence of amenorrhoea (21.1% in Implanon users versus 4.7% in Norplant users) and infrequent bleeding (27.3 % in Implanon users versus 21.1% in Norplant users), but no difference in frequent bleeding (6.1% versus 3.4%) or in prolonged bleeding (12.1% versus 9.0%) at 2 years.[354*][EL=1-]

About 40% of women experienced mild or severe dysmenorrhoea at entry to the study. The incidence of dysmenorrhoea changed from 59% and 51% at baseline to 9% and 21% at removal in the Implanon and Norplant group respectively.[358*355*][EL=1-]

(See 7.3)

Implanon

A retrospective chart review (n=132) in the UK reported a removal rate of 12% among Implanon users due to bleeding problems as the primary reason at 3 years. Bleeding disturbances were reported by 26% of Implanon users. They included prolonged bleeding (31%), oligo-amenorrhoea/amenorrhoea (27%) and irregular bleeding (13%). Normal cycles were reported in 28% of Implanon users at 3 years. [368][EL=3]

A multicentre non-comparative study (n=1183) in Switzerland reported discontinuation due to bleeding disturbances (45%). Side effects related to bleeding included infrequent bleeding (28%), amenorrhoea (33%), prolonged bleeding (15%) and metromenorrhagia (16%) at 1 year. [375][EL=3]

A non-comparative study (n=60) in Spain reported normal cycles (50%), infrequent bleeding (16%), frequent bleeding (3%), prolonged bleeding (5%) and amenorrhoea (12%) among Implanon users at 1 year. [367][EL=3]

A non-comparative study (n=108) in France reported that menstrual disturbances occurred in 83% of the women, mainly amenorrhoea (26%) and irregular bleeding (40%) at 20 months.[376][EL=3]

Norplant versus other contraceptive methods

One US cohort study compared Norplant (n=58) with DMPA (n=66) and combined oral contraceptives (n=75) in adolescent users. Amenorrhoea was reported in 36%, 60% and 8% of users of Norplant, DMPA and COC respectively at 6 months. The figures for regular menses were 0% versus 0% versus 92% and irregular bleeding 29% versus 10% versus 8% in these 3

groups. [288][EL=2-] More than 80% of Norplant and DMPA users experienced disrupted cycles and 80% of COC users maintained regular menstrual cycles at 6 months.

Another cohort study compared Norplant and Nova-T IUD. It reported a significant difference in dysmenorrhoea and increased menstrual flow (6% and 14% in Norplant users versus 33% and 43% in IUD users respectively at 1 year).[370][EL=2-]

A 5 year multicentre controlled cohort study (n=16,021) reported bleeding problems (characterised as excessive, irregular or both) occurring at a rate of 64/1000 women-years among users of Norplant, as compared with 25/1000 women-years in IUD users and 7/1000 women-years in sterilised women. Despite the frequency of the diagnosis, there was no difference in the rates of excessive bleeding requiring hospitalisation between Norplant users and controls (IUD users and women who were sterilised) (0.2 versus 0.2 per 1000 woman years; adjusted RR 1.36, 95% CI 0.49 to 3.75). The rate of amenorrhoea was significantly higher in Norplant users than controls (15.5 versus 3.3 per 1000 woman years; adjusted RR 5.08 (95% CI 4.16 to 6.20). Norplant users were significantly less likely to report dysmenorrhoea than women using IUDs and women who were sterilised (1.5 versus 3.3 versus 11.8 per 1000 woman years; adjusted RR 0.33, 95% CI 0.24 to 0.45).[174;369][EL = 3] This cohort study reported no difference in haemoglobin value of <10 g/dL between Norplant users and controls (IUD users and sterilisation) (1.5 versus 1.9 per 1000 woman years; adjusted RR 0.80, 95%CI 0.56 to 1.16).[174][EL=2+]

Summary of Evidence

- **Many women using Implanon will experience a change in bleeding pattern:**
- **Approximately 20% of users will experience amenorrhoea;**
- **Approximately 45% of users will experience either infrequent, frequent, or prolonged bleeding.**

- **Dysmenorrhoea is significantly reduced.**
- **As levonogestrel concentrations fall with time and ovulation becomes more likely among Norplant users, bleeding episodes tend to become more regular. Since the effect of Implanon on ovulation inhibition is consistent for all three years of use, bleeding patterns are unlikely to change with time.**

Recommendations:
Women should be advised that it is highly likely that their bleeding pattern will change while using Implanon. [C]

One in five women will have no bleeding while almost half will have frequent, infrequent or prolonged bleeding with Implanon use. Women should be advised that bleeding patterns are unlikely to become more regular over time. [C]

Women should be advised that dysmenorrhoea may improve during Implanon use. [C]

Management of bleeding problems
We did not identify any studies which assessed the management of bleeding problems in Implanon users.

Norplant

Mefenamic acid
A RCT compared the non-steroidal anti-inflammatory agent mefenamic acid with placebo in Norplant users. Bleeding was stopped in a significantly higher number of women in the mefenamic group (n=34) than in the placebo group (n=33)(76% versus 27%) at 1 week and 4 weeks (68% versus 33%). There was a significant decrease in mean number of days of bleeding in the mefenamic group when compared with the placebo group (11.6 ± 8.2 versus 17.2 ± 10.2) at 4 weeks.[380][EL=1+]

Ethinylestradiol

One RCT compared a levonorgestrel-containing COC versus ethinylestradiol alone versus placebo in Norplant users. The mean number of bleeding days was significantly lower in the COC group (n=45) than in the ethinylestradiol group (n=43) and in the placebo group (n=46)(2.6 ± 1.4 versus 5.4 ± 5.1 versus 12.3 ± 5.4). Bleeding stopped within 7 days in 2%, 14% and 50% of the COC, ethinylestradiol and the placebo group respectively. The COC was more effective than ethinylestradiol alone.[381][EL=1+]

Preliminary results from another RCT reported a significant reduction in the mean number of bleeding days at 3 months in Norplant users treated with either ethinylestradiol (n=18) or the combined pill (n=16) when compared with placebo (n=14)(19.2 ± 3.4 versus 18.2 ± 1.9 versus 28.6 ± 5.4).[382][EL=1+]

A RCT reported no significant difference in the clinical improvement of bleeding problems in Norplant users with a transdermal estradiol patch (n=33) when compared with a placebo patch (n=31)(70% versus 42%).[383][EL=1+]

Vitamin E

Preliminary results from a RCT reported a significant reduction in the mean number of bleeding days in Norplant users treated with vitamin E (n=38) supplementation when compared with a placebo (n=34)(7.7 ± 1.4 days versus 12.1 ± 1.3 days).[384][EL=1+]

A multicentre RCT compared vitamin E (n=120) , aspirin (n=122), vitamin E and aspirin (n=121) and placebo (n=123) in the treatment of Norplant-induced prolonged vaginal bleeding. No significant reduction occurred in the length and duration of bleeding/spotting episodes or bleeding-free intervals with any of these treatments in Norplant users.[385][EL=1-]

Anti-progesterone: Mifepristone

One RCT compared mifepristone and placebo in the treatment of bleeding disturbances among Norplant users during the first year of use. It reported that all women, regardless of treatment, experienced significantly reduced frequency of bleeding over the one year of observation. Women who received mifepristone treatment (n=50) reported significantly shorter episodes of bleeding when compared with the placebo group (n=50)(48 ± 15 vs 51 ± 15 days) during the first 90 days. There was a significant reduction in the average duration of bleeding episodes between the two groups (a mean of 14 days before treatment to 6.5 days in the mifepristone group vs 15 days to 11.1 days).[386][EL=1+]

Another RCT reported the same frequency of bleeding/spotting episodes but significantly less prolonged bleeding episodes in Norplant users receiving mifepristone (n= 58) when compared with the placebo group (n=57)(11 ± 3 vs 22 ± 23 days). The total number of bleeding days was 35% lower than in the placebo group. [387][EL=1+]

Summary of evidence

- **There is some evidence to support a beneficial effect of mefenamic acid or ethinylestradiol, alone or as an OC, or mifepristone on bleeding patterns in Norplant users. It is biologically plausible that the same will be true for Implanon.**
- **There is no evidence to support the use of Vitamin E or aspirin, and insufficient evidence for NSAID use in managing abnormal bleeding.**
- **There are no data on long term treatment.**

Recommendation:

Health professionals should be advised that non-hormonal treatment with mefenamic acid or hormonal treatment with ethinylestradiol or mifepristone is moderately effective in stopping irregular bleeding during implant use. [B]

7.5 Common concerns and symptoms

7.5.1 Weight change

Weight fluctuation in women of reproductive age is common. Many women are concerned that hormonal contraceptive use can lead to weight gain.

Implanon versus Norplant

A meta-analysis reported weight increase (of >10% from baseline at least once during implant use) in 8.7% of Implanon and Norplant users at 4 years.[354*][EL=1-]

Implanon

A retrospective chart review (n=132) in the UK reported weight gain in 4% in Implanon users at 3 years. [368][EL=3]

A multicentre non-comparative study (n=1183) in Switzerland reported weight gain in 9% of Implanon users at 1 year. [375][EL=3]

A non-comparative study (n=60) in Spain reported no significant changes from basline in mean weight among Implanon users at 6 months. [367][EL=3]

A non-comparative study (n=108) in France reported weight gain and weight loss in 37% and 11% respectively, of Implanon users at 20 months. [376][EL=3]

Norplant versus other contraceptive methods

A 5 year multicentre controlled cohort study (n=16,021 women), undertaken mainly in developing countries, reported a significant difference in the rate of reported weight gain (4.5 versus 0.9 per 1000 woman years; adjusted rate ratios 6.94, 95% CI 4.57 to 10.5) and weight loss (1.2 versus 0.5 per 1000 woman years; adjusted rate ratios 2.64, 95% CI 1.49 to 4.67) in Norplant

users when compared with controls (IUD users and sterilisation) at 5 years.[112][EL=2+]

One US cohort study compared Norplant (n=58) with DMPA (n=66) and combined oral contraceptives (n=75) in adolescent users. It reported no difference of change in body mass index from baseline in the three groups at 6 months.[288][EL=2-]

Another cohort study which compared Norplant (n=36) and Nova-T IUD (likely to be formerly Novagard, copper surface 200, discontinued in 2001)(n=23) reported no differences in weight change between the two groups at 1 year.[370][EL=2-]

Summary of Evidence

- **There are conflicting data that the use of implants is associated with weight change. However:**
- **In the short-term, there is no evidence for weight gain;**
- **Non-comparative studies reported weight changes of between 4-37% among Implanon users.**

Recommendation:

Women should be informed that the use of Implanon is not associated with weight changes in the short-term. [C]

7.5.2 Altered mood

We did not identify any studies which assessed the effect of Implanon on mood changes.

Implanon

A retrospective chart review (n=132) in the UK reported mood changes in 11% of Implanon users at 3 years. As the primary reason, severe mood changes accounted for 9% of all Implanon removals. [368][EL=3]

A multicentre non-comparative study (n=1183) in Switzerland reported mood swings and depressive mood in 5% and 3% respectively of Implanon users at 1 year. [375][EL=3]

A non-comparative study (n=60) in Spain reported nervousness in 2% of Implanon users at 1 year. [367][EL=3]

A non-comparative study (n=108) in France reported the occurrence of sad mood in 10% of Implanon users at 20 months. [376][EL=3]

A 5-year multicentre controlled cohort study (n=16,021 women) reported a significant difference in the incidence of mood disorders between Norplant users and controls (IUD users and sterilisation) (2.8 versus 1.2 versus 2.2 per 1000 woman years; adjusted RR 2.15, 95% CI 1.53 to 3.02).[112][EL=2+]

Summary of evidence

- **Observational studies reported mood changes ranging from 2-11% in Implanon users.**

Recommendation:

Women should be informed that mood changes may occur with the use of Implanon. [C]

7.5.3 Altered libido

The experience of sexual dysfunction, such as loss of libido, is common among young women, and the incidence ranges from 5% to 30%.[167;168]

A meta-analysis of clinical trials reported incidences of emotional lability and decreased libido of 4.9% and 3.3% in Implanon users versus 7.6% and 5.4% in Norplant users.[354*][EL=1-]

Implanon

A retrospective chart review (n=132) in the UK reported loss of libido in 1% of Implanon users at 3 years. [368][EL=3]

A multicentre non-comparative study (n=1183) in Switzerland reported loss of libido in 5% of Implanon users at 1 year. [375][EL=3]

A non-comparative study (n=108) in France reported that low libido did not occur among Implanon users at 20 months. [376][EL=3]

Summary of evidence

- **There is no evidence to support a change in libido for users of Implanon.**

Recommendation:

Women should be reassured that Implanon use is not associated with a change in libido. [C]

7.5.4 Acne

Acne is a common skin condition affecting 35% to 90% of adolescents.[290] Progestogens, particularly the more androgenic ones such as LNG, are a potent stimulus to sebum secretion which tends to make the skin greasier and prone to acne.[244] In contrast, the combined oral contraceptive is beneficial for acne; so women who change from a combined method to a progestogen-only method may notice an increase in acne.

Implanon versus Norplant

A meta-analysis of clinical trials reported an incidence of acne of 18.5% and 21.2% of Implanon and Norplant users (aged 18-40) respectively. No baseline data were available.[354*][EL=1-]

Implanon

A multicentre non-comparative study (n=1183) in Switzerland reported acne in 12% of Implanon users at 1 year. [375][EL=3]

A non-comparative study (n=60) in Spain reported acne in 11% of Implanon users at 1 year. [367][EL=3]

A non-comparative study (n=108) in France reported the occurrence of acne in 9% and the worsening of acne in 4% of Implanon users at 20 months. [376][EL=3]

Norplant versus other contraceptive methods

A 5-year cohort study (n=16,021 women) reported that Norplant users were significantly more likely to report acne than the controls (IUD users and sterilisation)(0.9 versus 0.2 versus 0 per 1000 women-years; adjusted RR 7.48, 95% CI 2.90 to 19.3).[112][EL=2+]

One US cohort study compared Norplant (n=58) with DMPA (n=66) and combined oral contraceptives (n=75) in adolescent users. It reported no difference in the occurrence of acne at 6 months in the three groups.[288][EL=2-]

Summary of evidence

- **One study suggested that Norplant increases the incidence of acne.**
- **Non-comparative studies reported the occurrence of acne in around 10% of Implanon users.**

Recommendation:

Women should be informed that acne may occur during Implanon use. [C]

7.5.5 Headache

Headache is one of the commonest symptoms experienced in the general population, both in young people and in adults. About 70% of adults report headache in the previous 3 months; the prevalence is greater in females than in males.[245] The prevalence of migraine is estimated to be about 7% among adolescents.[291]

Implanon

A retrospective chart review (n=132) in the UK reported headaches in 1% of Implanon users at 3 years. [368][EL=3]

A non-comparative study (n=60) in Spain reported headaches/migraines in 5% of Implanon users at 1 year. [367][EL=3]

Implanon versus Norplant

A meta-analysis of clinical trials reported incidences of headache in 16.8% versus 20.1% of Implanon and Norplant users respectively.[354*][EL=1-]

Implanon

A multicentre non-comparative study (n=1183) in Switzerland reported headches in 5% of Implanon users at 1 year. [375][EL=3]

Norplant versus other contraceptive methods

A 5-year cohort study (n=16,021 women) reported that Norplant users were significantly more likely than controls (IUD users and sterilisation) to report migraine/headaches (11.5 versus 2.1 versus 10.6 per 1000 women-years; adjusted RR 3.44, 95% CI 2.83 to 4.18).[112][EL=2+]

One US cohort study compared Norplant (n=58) with DMPA (n=66) and combined oral contraceptives (n=75) in adolescent users. It reported no difference with regards to headaches among the three groups at 6

months.[288][EL=2-]

Summary of evidence

- **The available evidence is inconclusive on whether or not subdermal implants increase the incidence of headaches.**
- **There is no evidence that instances of headaches are increased in women who use Implanon.**

Recommendation:
Women should be informed that all progestogen-only methods may be used by women who have migraine with or without aura. Women should be reassured that there is no evidence that headaches will be increased by the use of Implanon. [C]

7.6 Risks

7.6.1 Cardiovascular disease

Oestrogen-containing hormonal contraceptives are associated with an increased incidence of VTE. Concern has also been raised regarding coronary artery disease and the association of metabolic alterations caused by hormonal contraceptives. POICs do not appear to be associated with an increased risk of cardiovascular disease.

Implanon

A non-comparative study (n=60) in Spain reported no clinical significant changes in blood pressures, blood cholesterol and glucose concentrations among Implanon users at 1 year. [367][EL=3]

Implanon versus Norplant

One RCT (n=86) reported similar small effects on the haemostatic system among both Implanon and Norplant users. These effects are not suggestive of

an increased tendency towards thrombosis.[388][EL=1+]

A meta-analysis of clinical trials reported a low incidence of increased blood pressure in both Implanon and Norplant users. There was an increase of 0.1% versus 0.9% in systolic and 0.4% versus 0.7% in diastolic blood pressure in Implanon and Norplant users respectively.[354;357*][EL=1-]

The risk of cardiovascular disease and serum lipid profile may be related. One RCT (n=60) reported no significant difference in the change of apolipoproteins at 2 years from baseline among both Implanon and Norplant users.[389][EL=1-]

Another RCT (n=90) reported small changes from baseline in circulation concentrations of lipids and apolipoproteins. There was no significant change in these parameters among either Implanon or Norplant users at 3 years.[390][EL=1-]

One RCT (n=80) reported no significant changes in serum lipid ratios among Implanon and Norplant users at 2 years.[391][EL=1-]

Alterations in glucose and insulin levels may be related to the risk of cardiovascular disease.[392] A RCT (n=80) reported that both Implanon and Norplant induced mild insulin resistance. Although there was a significant increase in serum glucose levels from baseline in the two groups (values well within the WHO criteria for impaired glucose tolerance), there were no significant differences in changes in serum glucose levels between the two groups at 6, 12 and 24 months.[393][EL=1-]

Norplant versus other contraceptive methods

A 5-year multicentre controlled cohort study (n=16,021 women) reported no significant difference in the incidence of hypertension in the Norplant group versus controls (IUD users and sterilisation) (0.7 versus 0.4 versus 0.5 per 1000 women-years; adjusted RR 1.78, 95% CI 0.93 to 3.40). This study reported 2 cases of stroke and one case of deep vein thrombosis in the

Norplant group.[112][EL=2+]

In the absence of data on Implanon, the GDG considered it was appropriate to extrapolate from Norplant.

One US cohort study compared Norplant (n=58) with DMPA (n=66) and combined oral contraceptives (n=75) in adolescent users. It reported no difference of change in blood pressure measurements in the three groups at 6 months.[288][EL=2-]

Summary of evidence

- **There is no evidence for an adverse effect of contraceptive implants on blood pressure, risk of VTE or on known biomedical markers for increased risk of cardiovascular disease.**
- **Implants are assigned category '1' for healthy women aged from menarche to > 45 years in the current WHOMEC recommendations.**
- **Women with existing arterial disease can consider using all methods (Implants are assigned category '2' for initiation in women with current and history of arterial cardiovascular disease and hypertension and stroke; category '3' for continuation in the current WHOMEC recommendations.)**

Recommendation:

Subdermal implants are medically safe for women to use if there is a contraindication to oestrogen. [C]

7.6.2 Bone mineral density

There has been concern about the potential effects of POICs on bone mineral density (BMD), particularly among young women who have not yet reached peak bone mass and among older women, who may be starting to lose bone mass.[394] There is an association between the suppressive effect of

progestogen on ovarian oestrogen secretion and bone loss.[395] The evidence to date on whether or not subdermal implants cause a reduction in BMD is inconclusive.

Implanon

A systematic review to update the current WHOMEC recommendations reported no evidence of an adverse effect on BMD among healthy Implanon users.[377][EL=1-3]

Implanon versus other contraceptive methods

A cohort study (n=73) which compared Implanon with a copper IUD reported no significant difference in changes from baseline in BMD in both groups over a period of two years. The clinically significant mean decrease in BMD of one standard deviation was not reached at any point.[396][EL=2+]

Summary of evidence

- **There is no evidence for a clinically significant effect of Implanon on BMD.**

Recommendation:

Women should be informed that there is no evidence for a clinically significant effect of Implanon on bone mineral density. [C]

7.6.3 Ectopic pregnancy

The risk of ectopic pregnancy increases with the age of the women and the incidence ranged from 3 to 4.5 per 1000 women years among non-contraceptors.[173] Since ovulation is inhibited throughout the 3 years of use, the risk of ectopic pregnancy among Implanon users should be significantly less than that for women not using contraception.

We did not identify any studies which assessed the occurrence of ectopic pregnancy in Implanon users.

A 5 year multicentre controlled cohort study (n=16,021 women), undertaken mainly in developing countries, reported an ectopic pregnancy rate of 0.30, 0.68 and 0.13 per 1000 women-years in users of Norplant, copper-IUDs and sterilisation.[112][EL=2+]

One multinational RCT comparing Jadelle (n=598) and Norplant (n=600) reported an ectopic pregnancy rate of 0.4 per 1000 in the Jadell group versus 0 in the Norplant group at 5 years.[397][EL=1-]

A US non-comparative study of a variant of LNG capsule implants (n=511) reported an ectopic pregnancy rate of 0.6 per 1000 women years at 5 years.[61][EL=3]

Summary of evidence

- **No studies were identified looking at ectopic pregnancy and Implanon use.**
- **The level of ectopic pregnancy in other subdermal implants which do not always block ovulation is extremely low.**
- **On theoretical grounds, there would be a rate even lower for Implanon which blocks ovulation.**

Recommendation:

Women should be informed that the risk of ectopic pregnancy while using Implanon is theoretically extremely low, and less than that of women not using contraception. [C]

7.6.4 Women who become pregnant while using implants

The WHOMEC states that if a woman using progestogen-only implants is found to be pregnant, there is no known harm to the woman, the course of her

pregnancy or the fetus.[16][EL=4] However, if she plans to continue the pregnancy the implant should be removed as soon as possible as virilisation of the fetus may theoretically occur.

Recommendation:
Providers and women should be advised that there is no evidence for a teratogenic effect of Implanon. Nevertheless, should pregnancy occur and be continued, the implant should be removed. [D/GPP]

7.7 Return to fertility

Most studies show a rapid return of ovulation after removal of subdermal implants and no evidence of impaired fertility.

Implanon versus Norplant

A meta-analysis of clinical trials reported return of ovulation (indicated by ultrasound scan and/or serum progesteron >16 mmol/l) within 3 weeks in 93.6% versus 90.9% of women after Implanon and Norplant removal respectively.[354*][EL=1-].

Norplant versus other contraceptive methods

One cohort study reported a cumulative pregnancy rate of 76% and 70% in ex-Norplant users (n=51) and ex-DMPA users (n=47) respectively at 1 year. The corresponding figures were 90% and 89% respectively at 2 years.[335][EL=2-]

Another cohort study reported that pregnancy occurred in 96% of ex-Norplant users (n=87) compared with 100% of ex-copper IUDs (dose not stated)(n=44) at 2 years.[398][EL=2-]

A questionnaire survey of pregnant women (n=2841) in the UK evaluated the impact of contraceptive methods on subsequent fecundity. Conception rates

within 6 months of discontinuation were 71%, 77%, 27% and 25% among users of COC (n=925), IUDs (n=82), injectable (n=62) and implants (n=4) respectively, compared to 82% among condom users. [207][EL=3](see 4.8.2, 5.8 and 6.7.3)

Summary of evidence

- **There is evidence of rapid return to ovulation .**
- **No evidence of return to fertility for Implanon. The evidence for Norplant demonstrates no delay in the return of fertility. The GDG considered it appropriate to extrapolate.**

Recommendation:

There is no evidence for any delay in return of fertility following removal of contraceptive implants. [C]

7.8 Details of method use

7.8.1 Assessment prior to insertion

(See 3.6 for recommendations)

The UKSPR recommends that blood pressure screening is desirable before initiation of contraceptive implants. [78][EL=1-4]

7.8.2 Information prior to insertion

Recommendation:

Women should be advised of failure rates, benefits, risks and side effects of contraceptive implants. [D/GPP]

7.8.3 Time of insertion of implants

In a normal menstrual cycle

Guidance from the UKSPR stated that implants may be inserted at any time, if

it is reasonably certain that the woman is not pregnant. If the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be advised for 7 days following insertion.[399]

When switching method

The UKSPR recommends that contraceptive implants can be inserted immediately if the woman has been using her hormonal methods consistently and correctly or if it is reasonably certain that she is not pregnant.[78][EI=1-4]

Following termination of pregnancy

POSDI is assigned category '1' for insertion for women after first and second trimester abortion in the current WHOMEC. [16][EL=1-4] The RCOG Abortion guideline recommends that any chosen method of contraception should be initiated immediately following abortion.[213][EL=1-4]

Post delivery

An analysis of the pharmacokinetics of Implanon reported that serum ENG levels increased within 8 hours after Implanon insertion to concentrations associated with ovulation inhibition. Maximum mean serum concentration was reached after 4 days.[400;401][EL=3]

One RCT (n=250) compared the safety and tolerance of Norplant when inserted immediately post partum or 4 to 6 weeks post partum. The immediate insertion group reported significantly more bleeding days (28 ± 7.7 versus 22 ± 7.3 days) and headaches, but there was no significant differences in haemoglobin values at 4-6 weeks post partum between the two groups. These side effects did not appear to differ from a report in previous studies.[402][EL=1-]

POSDI is assigned category '1' for non-breastfeeding women (less and more than 21 days) post-partum in the current WHOMEC. [16][EL=1-4] (See section 7.10)

Recommendations:

Implants may be inserted at any time if it is reasonably certain that the woman is not pregnant. If the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be advised for 7 days following insertion. [D/GPP]

Implants may be inserted immediately following abortion in any trimester (spontaneous or induced). [D/GPP]

Implants may be initiated at any time post partum if it is reasonably certain the woman is not pregnant. [D/GPP]

7.8.4 Insertion and removal

We did not identify any studies which assessed the duration of Implanon insertion including consultation, insertion and women leaving the consulting room.

Complications of insertion and removal include pain at the site, physiological responses to a minor operation, and bruising. Complications at removal additionally include an inability to locate implants and broken implants. Since Norplant comprises six rods and Implanon only one, the incidence of problems associated in the insertion and removal is lower for Implanon.
A meta-analysis of clinical trials reported complications at insertion and removal of 0.3% versus 0% and 0.2% versus 4.8% for Implanon and Norplant respectively. Pain at the insertion site was the most frequently reported symptom, with incidences of 0.9% and 1.9% in the Implanon group and Norplant group respectively.[359][EL=1-]

Implanon was associated with a significantly lower frequency of removal

complications when compared with Norplant (0.2% versus 4.8%).[354*359*403*][EL=1-]

Complications included six deep insertions, six with fibrous adhesions, four where there was difficulty finding the implant and three broken implants in the Implanon group. In the Norplant group, four were broken implants, two were difficult to find and one was time-consuming. There was no report of expulsion of the device in the Implanon group and one reported expulsion with the Norplant group.[355*][EL=1-]

Summary of evidence

- **The risk of local discomfort and pain at insertion or removal is infrequent and is less than 1% for Implanon. Broken or non-palpable rods complicating removal occur less frequently with Implanon than Norplant. (0.2% compared to 4.8%).**
- **Immediate post-partum fitting of Norplant resulted in more bleeding days and headaches compared with delaying insertion to 4-6 weeks.**

Recommendations:

Women may be informed that Implanon insertion and removal both cause some discomfort and bruising but that technical problems are unusual (less than 1 in 100). [C]

Women should be informed that if an Implanon has migrated or is too deep to be removed, an ultrasound localisation and removal by an expert will be required. [D/GPP]

7.9 Training of health professionals

(See 3.14)

The FFPRHC provides training for health professionals wishing to obtain the Letter of Competence (LoC) in subdermal contraceptive implant techniques.

Adequate experience will be deemed to consist of a minimum of two insertions and two removals of subdermal implants over the 5-year recertification period. [404]

Recommendations:

Subdermal implants should be inserted and removed only by health professionals trained in the procedures. [D/GPP]

7.10 Specific groups

Adolescents

We did not identify any studies which assessed the use of Implanon among adolescents

Women over 35 years of age

A non-comparative study (n= 53) in Thailand assessed the use of Implanon in women over 35 years of age (mean age 39.7 years; mean BMI 24.9 ± 3.3) over 6 months. It reported no pregnancy. The most common side-effects reported were irregular bleeding (53 %) and amenorrhoea (35%). Regular cycles were reported in 11% of Implanon users. There was no change from baseline in diastolic pressure, body weight and BMI. The discontinuation rate was 8% at 6 months. [405][EL=3]

Adolescents versus adults

A cohort study (n=678) comparing side-effects and acceptability between adolescent users (13-18 years) and adult users (19-46 years) of Norplant reported no method failures in either group. There was no significant difference in concerns about irregular bleeding requiring clinic visits (57% of adolescent versus 38% of adult). The most common reason for implant removal was irregular bleeding (6% of adolescents versus 3% of adults

respectively). The overall discontinuation rates were 8% and 10% at 1 year and 11% in both groups at 18 months respectively.[406][EL=2-]

Another cohort study (n=1688; 45,576 woman months) reported no significant difference in discontinuation rates between adolescent users (n=674) and adult users (n=1014) of Norplant at 50 months. There were no significant differences in the primary reason for implant removal in both groups (irregular bleeding 28%, headaches 20% and local arm irritation or pain 16%). There were two pregnancies (failure rate of 0.11%), but it was not clear in the study in which group the pregnancies occurred.[407][EL=2-]

Norplant versus other contraceptive methods

A case-control study (n=112) which compared adolescents (11-18 years) who used Norplant or COC reported a significant difference in the pregnancy rate (0% versus 25%) and in discontinuation rates (9% & versus 66%) at 12 month follow-up. Menstrual irregularity occurred significantly more often among Norplant users than COC users (73% versus 5%). No significant difference was detected between Norplant and COC users in the reporting of weight gain (60% versus 53%), headaches (26% versus 42%), emotional problems (26% versus 5%) and amenorrhoea (6% versus 0%). Objective measurements of weight and body mass index showed weight gain in both groups (4 kg in Norplant users versus 2 kg in COC users) at 12 months. Weight gain in excess of 9.1 kg was limited to Norplant users.[408][EL=2-]

A cohort study (n=166) in the US reported a significant difference in pregnancy rates among adolescents (12 to 18 years) who were using Norplant, Combined Oral Contraceptives (COC) or other methods (condoms or no methods) (2% versus 13% and 17% respectively during the 1 year study period). Norplant users were significantly more likely to continue with the method than COC users (87% versus 50%) despite similar satisfaction scores at 6 months. There was a significant difference between Norplant and OC users and other methods (condoms or no methods) in reports of irregular bleeding (89% versus 59% versus 54%), headaches (39% versus 37% versus

10%), mood swings (54% versus 32% versus 25%), acne (30% versus 12% versus 10%) and hair loss (15% versus 0% versus 0%). The difference in weight gain was not significant (52% versus 40% versus 42%). The most common reason given for discontinuing Norplant was menstrual irregularity (71%).[409][EL=2-]

Another cohort study (n=199) of adolescents (11 to 20 years) reported no difference between the three groups in headaches, depression, acne and weight gain. Over 80% of DMPA and Norplant users reported irregular menstrual bleeding versus 90% of COC users experiencing regular cycles at 6 months.[288][EL=2-]

A cohort study (n=48) of adolescents (12 to 21 years) reported no significant differences in BMD among Norplant users, DMPA users, OC users and controls (no hormonal methods) at 1 year. There were significant differences in BMD among the groups at 2 years (a total increase of 9.3% in Norplant users, total decrease of 3.1% in DMPA users and a total increase of 9.5% in the controls).[317][EL=2-]

A cohort study (n=98) amongst postpartum adolescent mothers (at or under 17 years) in the US reported that the main reasons for choosing Norplant were: difficulty remembering to take the pills (71%), side effects of OC (38%), fear of pregnancy (57%), ease of use of Norplant (48%) and encouragement from others (34%). Seventy-four percent of Norplant users were 'very satisfied' with the implant and 95% would recommend its use as compared to 38% and 79% respectively in the OC users. There was a significant difference in discontinuation rates (5% versus 33% in Norplant and COC users respectively at 15 months.[410][E=2-]

A US questionnaire survey (n=112) of adolescents (13 to 20 years), including mothers, reported a high level of interest (over 70%) in Norplant because of its contraceptive effectiveness and convenience. The most undesirable side-effects were acne, headaches, weight and menstrual changes, reported by 87%, 83%, 71% and 71% of the adolescents respectively. One prior

pregnancy was the main characteristic predictive of a high level of interest in Norplant.[411][EL=3]

Norplant is assigned category '1' for women aged under 18 in the current WHOMEC recommendations.[172][EL=2-]

Summary of evidence

- **There is no evidence for any difference in side-effects or reasons for discontinuation among adolescents compared with adults.**
- **There is evidence for lower pregnancy rates in adolescents compared with use of pills and condoms.**
- **There is no evidence for effectiveness or adverse effects between different age groups**

Recommendations:

Women and adolescents should be informed that there is no evidence that effectiveness or adverse effects of implants vary with the age of the user. However, STI risk and Fraser competence (for adolescents) should be considered. [C]

Providers and adolescents should be aware that pregnancy rates are lower among adolescents using implants compared with those using oral contraception or condoms. [C]

Women with body mass index over 30

There have been concerns that the efficacy of some progestogen-only methods may be compromised in heavier women.

A meta-analysis of clinical trials reported no pregnancies among Implanon users weighing ≥ 70kg at 1 year (n=161), 2 years (n=125) and 3 years (n=78).[354*][EL=3] However, the numbers in these trials were small.

Implanon is assigned category '1' for women with a BMI ≥ 30 kg/m2 in the current WHOMEC recommendations.[16][EL=2-]

Summary of evidence

- **From small studies, there is no decrease in efficacy for Implanon for women who weigh more than 70kg.**

Recommendation:

Women should be advised that, as potential users of Implanon, there is no evidence for a higher rate of pregnancy among women weighing over 70kg. [D/GPP]

Women who are breastfeeding

(Refer to 7.8.3)

Concern has been raised that hormonal methods of contraception interfere with milk production and have adverse effects on the baby.

A cohort study compared changes in the volume and composition of breast milk in breastfeeding women who elected to use Implanon (n=42) or non-hormonal IUD (n=38) at 6 weeks post partum. There were no significant changes between the 2 groups in milk content of fat, protein and lactose.[412][EL= 2-]

A cohort study (n=108) reported that initiation of Norplant in healthy lactating women around day 60 post partum had no deleterious effect on bone density measurements when compared with users of copper T 380A IUD and or progesterone-releasing vaginal rings at 1 year during lactation and 1 year after weaning.[413][EL=2+]

Beyond six weeks post partum, Implanon is assigned category '1'. Up to six weeks post partum WHOMEC considers Implanon a category '3'.[16] The FFPRHC does not support the latter view and recommends using local guidelines.

Summary of evidence

- **The GDG concluded that the evidence does not support the concerns that hormonal methods of contraception interfere with milk production and have adverse effects on the baby.**

Recommendation:

Subdermal implants can safely be used by women who are breastfeeding and may be inserted at any time post partum if there has been no risk of pregnancy. [D/GPP]

7.11 Medical conditions and contraindications

Women with pre-existing medical conditions and those taking enzyme-inducing drugs are almost always excluded from clinical trials.

Diabetes

Women with diabetes are at increased risk of cardiovascular disease. Concern about the effects on the cardiovascular system and on carbohydrate metabolism often deter doctors from prescribing hormonal methods of contraception.

We did not identify any studies which assessed the effect of Implanon use on women with diabetes.

A cohort study (n=80) compared glycaemic control, lipoprotein metabolism and coagulation profile in diabetic women using Norplant, DMPA, COC or IUD. It reported minimal alterations in Norplant users. There were small changes among COC users but the most significant changes occurred among users of DMPA.[229][EL=2-]

A systematic review (n=1 cohort study) to update the WHOMEC did not identify any study which assessed the effect of implants in women with

diabetes.[414][EL=3]

Norplant and Implanon are assigned category '1' rating for women with a history of gestational disease, '2' rating for women with insulin and non-insulin dependent diabetes in the current WHOMEC recommendations.[16][EL=2-]

Summary of evidence

- **There was no evidence of a significant disturbance to diabetic control in women using Norplant.**

Recommendation:
Women should be informed that Implanon is not contraindicated for women with diabetes. [C]

Epilepsy

A systematic review (n=1 cohort study and 2 case reports) conducted to update the WHOMEC reported conflicting evidence on the safety of concurrent use of an anti-epileptic drug and hormonal contraceptive methods. However, no harmful effect on epilepsy or seizure frequency was reported in this cohort study.[415;416][EL=2-]

Sexually transmitted infections, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)
(See 3.11)

A systematic review (n=2 non-comparative studies) conducted to update the WHOMEC reported that, in post-partum Norplant users with asymptomatic HIV-1 infection, the side-effect profiles are similar to those reported in other studies of non-infected women. No measures of disease progression were reported in these studies.[230][EL=3]

Norplant and Implanon are assigned category '1' for women who are HIV-

positive or with high risk of HIV in the current WHOMEC recommendations.[172][EL=2-]

Recommendation:

There is no evidence to suggest a causal relationship between the use of implants and an increased risk of STI or HIV acquisition. Women at increased risk of STI including HIV/AIDS may use implants. Subdermal implants do not protect against STI/HIV and if there is a risk, the correct and consistent use of condoms in addition to the implants is recommended. [D/GPP]

7.12 Drug Interactions

Some drugs, in particular certain anti-epileptic drugs, induce liver enzymes and thereby hasten the metabolism of steroid hormones. This has the effect of reducing serum levels and in the case of contraceptive steroids, this may lower contraceptive efficacy. (See under Epilepsy, Section 7.11)

We did not identify any studies which assessed drug interactions among Implanon users.

A systematic review (n=1 cohort study and 2 case reports) conducted to update the WHOMEC reported conflicting evidence on the safety of concurrent use of an anti-epileptic drug and hormonal contraceptive methods. The majority of the studies reviewed were methodologically flawed. Lower LNG serum levels and contraceptive efficacy were reported after Norplant insertion in women taking the anti-epileptic drugs phenytoin and carbamazepine, suggesting that Norplant may not be reliable in patients taking phenytoin and carbamazepine.[415;416][EL=2-]

Norplant and Implanon are assigned category ‘3’ for women taking the enzyme-inducers phenytoin, carbamazepine, barbiturates and primidone in the current WHOMEC recommendations.[16][EL=1-4]

Theoretical concerns exist about interactions between hormonal contraceptives and antiretroviral drugs. It is possible that the efficacy of both groups of drugs may be reduced. A systematic review undertaken by the WHOMEC 2004 concluded that insufficient published data exist to allow any recommendation to be made about the concurrent use of hormonal contraceptive and antiretrovirals.

Summary of evidence

- **Contraceptive implants may be associated with higher failure rates in women concurrently taking enzyme-inducing drugs.**

Recommendation:

Implanon is not recommended as the sole method of contraception for women concurrently taking enzyme-inducing drugs. [D/GPP]

7.13 Follow-up

The UKSPR recommends that no routine follow-up visit is required once Implanon has been inserted. Healthy implant users are advised to return at any time to discuss side-effects or other problems, or if they want to change the method, and to return when it is time to have the implant removed.[78][EL=1-4]

Recommendation:

No routine follow-up after implant insertion is required. [D/GPP]

7.14 Economic evidence

The economic analysis conducted for this guideline showed that the implant is more effective and more costly than male condom and COC for one year of use, incurring an additional cost equal to £378 and £405 per pregnancy

averted, respectively. For periods of contraceptive use equal to 2 years and above, the implant dominates both male condom and COC.

The implant is overall less effective than male and female sterilisation, due to high discontinuation rates associated with its use. Non-reversible contraceptive methods are more costly than the implant for short periods of use. However, they become the dominant options (both more effective and less costly) compared to the implant for periods of contraceptive use equal to 4 and 6 years for male and female sterilisation respectively, and above.

The implant dominates the injectable for 2-15 years of use (15 years was the maximum time frame considered in the analysis). For one year of use, the implant is more effective than the injectable at an additional cost of £4,141 per pregnancy averted.

The implant dominates IUS for short periods of use, up to 3 years, and also at 6 years of use. For the other time-frames examined, the implant is both more effective and more costly than the IUS, with ICERs ranging between £12,229 per pregnancy averted (at 4 years of use) and £741 per pregnancy averted (at 12 years of use), depending also on the times of re-insertion of the two methods.

Compared to IUD, the implant is constantly more effective and more costly across all time periods examined. For short periods of use up to 4 years, its ICER compared to IUD ranges from £21,526 (one year of use) to £42,252 (3 years of use) per pregnancy averted. This ratio falls to £10,312 per pregnancy averted at 5 years of use, and decreases thereafter, reaching a cost of £1,617 per pregnancy averted at 15 years of use, with slight increases at 10 and 13 years of use, due to implant re-insertion costs.

The cost-effectiveness of an implant relative to IUD and IUS is determined by the level of discontinuation associated with LARC use.

Evidence statement

- **The implant is more cost-effective compared to the male condom and COC, even for short periods of contraceptive use (1-2 years).**

- **Male and female sterilisation are more cost-effective than the implant for long periods of contraceptive use, starting from 4 and 6 years respectively and above.**

- **The implant is more cost-effective than the injectable for contraceptive use equal to 2 years and above. It is also more cost-effective than IUS for periods of use between 1 and 3 years, and also for 6 years of use. Compared to IUD, the implant is constantly more effective and more expensive across all time horizons examined. Nevertheless, relative cost-effectiveness of the implant compared to IUS and IUD is highly sensitive to changes in discontinuation rates associated with LARC use.**

Full results of the economic analysis are presented in Chapter 8.

8 Economic evaluation

8.1 Introduction – the role of health economics in the LARC guideline

The aim of the economic evaluation was to assess the cost-effectiveness of long-acting reversible contraceptive methods (LARC methods). However, the GDG felt that issues of cost-effectiveness should have a greatly reduced influence on any decisions regarding provision of contraception at an individual level: women's preferences, personal needs and acceptability were deemed fundamental in determining the final choice of contraceptive method. In chapter 3 it is recommended that "women and men should have access to all available types of licensed contraception and be free to choose the method that suits them best". Thus, the GDG has given greater significance to freedom of choice rather than cost-effectiveness when formulating recommendations. Nevertheless, the estimation of the cost-effectiveness of LARC methods was regarded as an important piece of information, especially for healthcare providers, as the high initial costs associated with most LARC methods (in particular the IUS and the implant) were believed to be among the main barriers to the availability of LARC methods in the NHS, contributing to their current low uptake.

Cost-effectiveness of LARC methods in the UK was evaluated in comparison to the male condom, the combined oral contraceptive pill (COC), and also non-reversible contraceptive methods, i.e. vasectomy and female sterilisation. The COC and non-reversible contraceptive methods were selected as comparators by the Guideline Development Group (GDG), with the justification that women of reproductive age who are likely to consider (and substantially benefit from) LARC as a contraceptive option are mainly those already using the COC, or those considering COC/non-reversible contraception as an alternative method. The male condom was chosen on the basis that it is the second commonest method of contraception after the pill in the UK[1]. In addition, comparisons of the relative cost-effectiveness between different LARC methods were undertaken.

In order to assess the cost-effectiveness of LARC methods a systematic literature review was undertaken along with a cost-effectiveness analysis based on a decision-analytic model that was developed for this purpose. The results of the literature review are presented first, focusing on the content, findings and limitations of UK-based studies. Then a description of the economic model used in the guideline is provided, including details on the rationale for the model, cost and effectiveness parameters considered, the design of the model, and the input values used. Finally, the results of the cost-effectiveness analysis are presented accompanied by evidence statements.

8.2 Literature review

A systematic review of economic studies was undertaken to evaluate the cost-effectiveness of LARC methods compared with other forms of contraception (details on the methodology adopted are provided in chapter 1). The total number of articles identified was 1083. All paper abstracts were reviewed, and 24 articles were retrieved and critically appraised. Fourteen articles were finally included in the review as relevant to the economic question. The design and the results of all studies included in the review are presented in the evidence tables. Eight of the studies were conducted in the US[417-424] and one in Thailand[425]. The general conclusion drawn by these studies was that all contraceptive methods provided substantial cost-savings compared to no method[417-421]. Female and male sterilisation were shown to be the most cost-effective methods (highest level of effectiveness at lowest cost) in the long term[420;422;423]. LARC methods were also highly cost-effective, especially IUDs and the IUS, followed by the injectable and the implant[420-423]. Two studies that assessed the cost-effectiveness of the implant showed that it depended highly on the duration of use of the method[424;425]. However, the above results refer to the specific context in which the studies were conducted. The health care systems of the US and Thailand differ from that of the UK in terms of organisation, access and resource use, and therefore conclusions derived from non-UK studies are of limited value in the UK context.

Five studies (one of which was an update of an earlier study using the same

methodology) were conducted in the UK, published from 1995 to 2004[125;426-429]. The methodology and results of these studies were used to inform the economic model developed for this guideline. Each study included an economic model, which incorporated effectiveness rates and costs associated with events related to contraceptive use, in order to estimate the relative cost-effectiveness of various contraceptive methods. All five studies adopted the NHS perspective. Table 8.1 shows the variables used in the economic models (in terms of cost and effectiveness) and the method of presentation of results in the UK based studies.

Note: The study by French et al used effectiveness rates derived from a meta-analysis that included also non-UK studies. However, the estimated costs reflected UK clinical practice, since they were based on UK resource use patterns and unit prices. Therefore, the French et al study was considered relevant to the UK context.

Table 8.1 Categories of input parameters and method of presentation of results in UK based studies

Author and date	Methods examined	Viewpoint and costs included/excluded	Effectiveness	Results	Comment
Varney & Guest, 2004 [429]	Comparisons between Implanon, IUS and injectable (DMPA)	NHS viewpoint, 2002-3 prices. Included: Method costs Healthcare resource use (primary care & outpatients) while using each method (treatment of side-effects & subsequent discontinuation partially included) Excluded: Costs of unintended pregnancies Costs of additional treatment of side effects Costs of switching to a new method after discontinuation	Number of pregnancies averted	Additional cost per additional pregnancy averted (incremental analysis)	Cost estimates based on actual resource use data, derived from a GP database Direct comparisons were made between the methods examined.

Phillips, 2000 [426]	Implanon compared with Norplant, and Mirena; further comparison with DMPA and COC.	NHS viewpoint, 1997-8 prices. Included: Method costs adjusted for discontinuations Savings due to pregnancies averted (compared to no method) Excluded: Costs associated with side-effects	Number of pregnancies averted compared to no method	Net savings per patient Additional cost per additional pregnancy averted in comparison to DMPA and COC (incremental analysis)	Comparisons were made between each method and no method. Direct comparison was made only between Implanon and DMPA, and also Implanon and COC.
McGuire & Hughes, 1995 [427] Hughes & McGuire, 1996 (updated study) [428]	Contraceptive methods available in the UK: OC, diaphragm, IUD, condom, injectable, spermicide, implant, vasectomy, female sterilisation.	NHS viewpoint, 1991 prices. Included: Method costs Savings due to pregnancies averted (compared to no method) Excluded: Costs associated with side-effects & discontinuations.	Number of pregnancies averted compared to no method	Net savings per pregnancy averted Net savings per adjusted couple year of protection (CYP)	Comparisons were made between each contraceptive method and no method.
French et al, 2000 [125]	Norplant compared with: IUD>250mm^2, IUD≤250mm^2, OC, DMPA. Mirena compared with: IUD>250mm^2, IUD≤250mm^2.	NHS viewpoint, 1998 prices. Included: Method costs (ingredient and health service resource use) Failure costs (associated with pregnancy outcomes) Excluded: Costs associated with side effects & discontinuations.	Number of pregnancies averted	Additional cost per additional pregnancy averted (incremental analysis)	Effectiveness rates based on a systematic review and meta-analysis. Direct comparisons were made between the methods examined.

8.2.1 Costs included and excluded in the UK-based studies

All UK studies included contraceptive method costs (ingredient costs and health service costs). With the exception of the study by Varney & Guest, the rest of the UK studies considered also the costs to the NHS associated with outcomes of unintended pregnancies due to contraceptive failure, i.e. live births, miscarriages and abortions. In some cases these costs were expressed as savings from unintended pregnancies averted by contraceptive use.

Other costs to the public purse such as social service expenditure and welfare payments, and costs to the women were not included in the cost-effectiveness analyses. Costs incurred during the life of a person born as a result of contraceptive failure (or the value of life foregone by contraceptive use) were not taken into account. In addition, adverse events and secondary beneficial effects of contraception were, in principle, not considered in the studies; however, Varney & Guest utilised actual resource use data (GP and practice nurse visits, as well as referrals to a gynaecologist outpatient clinic) in order to estimate total costs associated with contraceptive use. Therefore, it was likely that management of some side effects (such as those that did not require additional treatment, e.g. hospitalisation) was reflected in the total cost estimates.

With the exception of one study,[426] the additional costs associated with the discontinuation of a method were not taken into account. These costs refer to costs of starting a new contraceptive method (additional counselling and start-up costs) or costs associated with unintended pregnancies resulting from discontinuation and the subsequent use of a less effective contraceptive method (or no method).

8.2.2 Outcomes measured in the UK-based studies

The main measure of effectiveness was the number of pregnancies averted by one method compared with no method[426-428] or with another contraceptive method[125;429].

Preferences attached to different forms of contraception and issues related to quality of life were not examined in the studies reviewed. Moreover, issues concerned with the valuing of life forgone by contraceptive use, or life resulting from an unintended pregnancy that continues to live birth (for both the pregnant woman and the baby born), were not considered in this literature.

8.2.3 Presentation of the results

The cost-effectiveness results of the studies were reported using two different methodologies:

1. In the report by McGuire and Hughes[427] and their updated study[428], results were presented as "net savings (to the NHS) per pregnancy averted or per adjusted couple year of protection": these represented the actual savings to the NHS (savings from pregnancies averted minus method costs of contraception) associated with preventing one pregnancy by using a contraceptive method. In the study by Philips[426], results from the main comparisons (between two types of implant and the IUS) were presented as net savings per woman provided with a contraceptive method. In all cases contraceptive methods were compared to a 'no method' alternative. Therefore, all net savings per unit of effectiveness referred to the economic benefits of each contraceptive method examined against no method of contraception. Direct comparisons between different methods of contraception were not performed, i.e. the additional costs and benefits of switching between methods were not examined.

2. French et al[125] and Varney & Guest[429] reported the results as "additional costs per additional pregnancy averted" (incremental cost-effectiveness ratio) from switching between contraceptive methods, thus allowing for direct comparisons between different methods. Philips also used this methodology for a part of the analysis that directly compared Implanon with injectables and the combined oral contraceptive pill (COC)[426].

8.2.4 Overall findings from the UK-based literature

McGuire and Hughes[427;428] showed that all methods of contraception were cost-effective, providing net savings per pregnancy averted or per couple year of protection. However, the value of this analysis is limited in the context of this guideline, as it does not allow for direct comparisons between contraceptive methods so that their relative cost-effectiveness can be

assessed. Such an analysis is required in order to explore the resource consequences of switching between contraceptive methods that may differ in effectiveness but also in associated costs.

French et al[125] performed comparisons between different methods of contraception. The number of comparisons was limited since the analysis was based on a systematic review of studies meeting strict inclusion criteria. The main comparators were subdermal implants (Norplant) and intrauterine systems (Mirena). All comparisons showed that there were additional costs (ranging from £721 to £255,102) per pregnancy averted associated with switching to Norplant or Mirena from any other contraceptive method included in the analysis.

The study by Varney & Guest[429] made direct comparisons between the implant, the IUS and the injectable. The analysis demonstrated the injectable was dominated (i.e. was less effective and more costly) by both the implant and the IUS. The implant was more effective than the IUS, but at an additional cost of £20,953 per pregnancy averted; the authors concluded that the implant was likely to be less cost-effective than IUS, as they considered the additional cost per additional pregnancy averted relatively high, compared to the cost of an unintended pregnancy to the NHS (£912). It is noted that costs of outcomes associated with unintended pregnancies due to contraceptive failure (i.e. live birth, miscarriage, abortion) were not included in the analysis.

The Philips study[426] demonstrated that LARC methods provided effective contraceptive protection and represented value for money from the perspective of the NHS. Implanon was reported to be more cost-effective than Norplant and Mirena in terms of cost per pregnancy avoided and cost per protected year; however, no direct comparisons were performed between these methods. The direct comparison between Implanon and Depo-Provera demonstrated that Implanon was both less costly and more effective. Finally, compared to COC, Implanon incurred an additional method cost of £616 per additional pregnancy averted (in this case, costs associated with the discontinuation of COC were not taken into account).

8.2.5 Limitations of UK-based literature

The UK-based studies are characterised by a number of limitations. All studies were based on models that did not incorporate events such as discontinuation of contraceptive method (with the exception of the study by Philips[426]) and adverse effects (with the exception of the study by Varney & Guest[429]), in which some costs of treating side-effects were included). Both types of events are regarded as important parameters in the use of LARC methods, which may affect their relative cost-effectiveness.

In the context of LARC method use, discontinuation of a method is an important issue since it is likely to lead to the use of a less effective method or no use of contraception and consequently to more unintended pregnancies. Moreover, methods with a long duration of effectiveness that carry relatively high initial costs, such as the implant, the IUS or the IUDs, require a substantial period of use so that their higher level of effectiveness in the longer term offsets their initial costs. For these reasons, and since it was found that LARC methods were related to high discontinuation rates, the omission of discontinuation rates in the estimation of cost-effectiveness of LARC methods was considered to be a limitation of the UK studies.

Adverse effects may also have an impact on the relative cost-effectiveness of LARC methods if they lead to additional healthcare resource use (e.g. additional GP consultations for treatment or hospitalisation). Nevertheless, costs associated with the management of side-effects of contraceptive use were also not considered in the majority of the UK studies.

Finally, direct comparisons between contraceptive methods were very limited in this literature. Therefore, the impact of switching from one contraceptive method to another in terms of incremental costs to the NHS and contraceptive benefits to the users was not investigated.

8.3 Development of a model for the economic evaluation of LARC methods

8.3.1 Rationale for the model

An economic model was developed in order to examine the cost-effectiveness of LARC methods based on the clinical effectiveness data presented in this guideline. Direct comparisons were made across different LARC methods, and also between LARC methods and other forms of contraception that the GDG considered as relevant alternatives to LARC methods: the male condom, the combined oral contraceptive pill (COC) and non-reversible methods (male and female sterilisation). Consequently, the economic analysis undertaken for the guideline examined the relative cost-effectiveness of switching from one contraceptive method to another. The cost-effectiveness of using a specific contraceptive method versus use of no method was not determined.

The economic model was intended to overcome some of the limitations identified in the previously published studies, by incorporating parameters such as discontinuation rates, and frequency and cost of side-effects of contraceptive use, which were thought to affect the relative cost-effectiveness between contraceptive methods. In the case of side-effects, estimation of management costs was not feasible, as there were not reliable data on the frequency of side effects that required additional healthcare resource use (e.g. GP consultations), and the associated costs of clinical management. It is recognised that omission of costs associated with the management of side-effects from the model structure constitutes a limitation of the analysis. Nevertheless, it was possible to include discontinuation rates in the development of the economic model, based on data reported in the guideline. Although not all side-effects lead to discontinuation, and, reversely, not all discontinuations occur as a result of side-effects, it is well established that a significant proportion of discontinuations is due to side-effects, and in this sense the incidence of side-effects following contraceptive use was partially reflected in discontinuation rates. Therefore, the relative cost-effectiveness

between contraceptive methods was determined not only by clinical effectiveness, but also by the rates of discontinuation characterising each method.

Finally, an update of cost and effectiveness data was considered useful, since some of the UK studies were based on data collected up to 10 years ago.

8.3.2 Cost and outcome parameters considered in the model

The perspective adopted in the economic analysis was that of the NHS. Costs included in the model consisted of method costs (ingredient and health service costs), as well as costs due to contraceptive failure (unintended pregnancy and its consequences). Costs associated with clinical management of adverse effects were not considered in the analysis, since no relevant data could be identified in the published literature.

Non-contraceptive beneficial effects and associated cost-savings (e.g. the reduction in need for surgical treatment of menorrhagia following IUS use[430] and the protective role of male condom against sexually transmitted infections -STIs-) were not considered in the estimation of costs, as relevant data were difficult to identify, and beneficial non-contraceptive effects were not included in the scope of the guideline.

The societal costs associated with unintended pregnancies (e.g. income maintenance payments and costs of adoptions arising from unintended pregnancies) and indirect costs (productivity losses) were not examined in the economic model. The long-term costs and consequences arising from raising a child borne due to an unintended pregnancy were beyond the scope of the guideline and the economic analysis. Moreover, it would be necessary to consider both the future costs *and* benefits for the evaluation to be meaningful, and no straightforward and satisfactory way of identifying and measuring the future costs and benefits to society (associated with the termination of an unintended pregnancy or with a live birth resulting from it) was available to inform the analysis. Similarly, issues concerned with the

value of life forgone by contraceptive use, or life resulting from unintended pregnancy, were not considered in the economic analysis.

The costs of unintended pregnancy were estimated up to the birth of a viable baby (i.e. including costs of neonatal care until discharge of infants from hospital). All pregnancies were assumed to be unintended; no distinction was made between unwanted and unplanned pregnancies (in some of the published literature unintended pregnancies were divided between unwanted pregnancies that would never occur later in time, and unplanned or mistimed pregnancies that would occur sometime later in the future[431-434]). This classification has been used mainly by non-UK economic studies on contraception for the estimation of cost savings due to contraceptive use. In the case of unwanted pregnancies, cost savings included the total cost of an unwanted birth, whereas in the case of unplanned pregnancies, cost savings were lower, and they occurred only because the cost of an unplanned birth was deferred to a later time (when pregnancy was planned)[417;418;420]. However, the GDG expressed the opined that both unwanted and unplanned births often result in an ultimate increase in the number of children in the family (i.e. an “unplanned” child born earlier than a woman/couple plans to have children usually does not reduce the number of “planned” children born in the future). Therefore, unwanted pregnancies were not distinguished from unplanned pregnancies in terms of associated costs of birth, and total costs of unintended births were included in the model.

Outcomes were expressed as the number of pregnancies averted by the use of one contraceptive method in comparison with another. The quality of life and users’ preferences related to contraceptive use were not included in the model due to lack of reliable data in the relevant literature.

8.3.3 Design of the model – basic assumptions

A decision-analytic Markov model was constructed in order to evaluate the cost-effectiveness of LARC. This type of model was considered appropriate as it allowed for a dynamic representation of the possible events associated

with use of a contraceptive method, i.e. contraceptive failure and pregnancy, discontinuation and switch to another contraceptive method/no method, or a combination of these events. Additionally, such an approach allowed for the evaluation of cost-effectiveness of LARC over different time frames.

The model was run in yearly cycles to assess whether the relative cost-effectiveness between methods changed over time. A hypothetical cohort of 1000 sexually active women of reproductive age adopted one contraceptive method at the beginning of the first year. The model was constructed so that every year a proportion of women discontinued the method and chose another method or no method summarised in “average contraceptive method”. The concept of an “average contraceptive method” was developed in order to consider the impact on cost-effectiveness of discontinuation itself rather than of the patterns related to contraceptive method switching. In addition, there were no comprehensive data on switching patterns for LARC methods in the UK context. A limitation of this approach was that it did not consider the fact that women who discontinue one method are not always eligible to use all other methods available. Women discontinuing IUD, for example, may not be able to use hormonal methods due to contraindications (which made them use an IUD in the first place).

The average contraceptive method included all contraceptive methods used in England and Wales. A weighted average failure rate was calculated taking into account failure rates for all contraceptive methods included, weighted by using the most recent data on contraceptive usage in England and Wales for women “at risk of pregnancy”[1;435]. Where failure rates were not reported in the guideline, these were derived from a published review[436]. A weighted average method cost was also calculated using the same approach.

Every year, each member of the hypothetical cohort of women faced two possible events:

1. contraceptive protection;
2. contraceptive failure and subsequent unintended pregnancy.

Four possible outcomes of unintended pregnancy were included in the model:

1. live birth;
2. miscarriage;
3. abortion;
4. ectopic pregnancy.

The probabilities of ectopic pregnancy resulting from contraceptive failure were specific to each method assessed. The relative probabilities for the remaining outcomes were assumed to be common for all methods.

Note: The proportion of ectopic pregnancies among all pregnancies due to contraceptive failure associated with some methods (IUS, IUD, female sterilisation) is higher than the respective proportion in the general population, thus affecting the results in terms of associated costs.

The following costs were estimated in the model:

1. method costs based on ingredient costs and health care resource use;
2. costs due to unintended pregnancy, related to all possible outcomes.

Outcomes were expressed as the number of unintended pregnancies due to contraceptive failure.

It was assumed that potential discontinuation of a LARC method and switching to the average contraceptive method occurred in the middle of each year, i.e. at 6 months. For the first 6 months, costs and contraceptive failure were attributed to the LARC method examined. For the last 6 months of the year (assumed to follow discontinuation), costs and contraceptive failure referred to the average contraceptive method.

The analysis considered different time frames, starting from one year and going up to 15 years of contraceptive use. The maximum time horizon of 15

years was selected because this was estimated to be the average duration of effect of female sterilisation, which was one of the comparators to LARC methods used in the model. It was felt by the GDG that a comparison between LARC methods and female sterilisation should consider the full contraceptive benefit provided by female sterilisation. Ultimately, the time frame of one to maximum 15 years of contraceptive use was also chosen for the rest of comparisons performed in the analysis.

A schematic diagram showing the structure of the decision-analytic model used for the economic analysis is presented in Appendix B.

8.3.4 Contraceptive methods examined in the model

The LARC methods evaluated in the economic analysis were:

1. IUD: The analysis was based on T-Safe use (regarding cost and effectiveness data utilised). The analysis considered duration of use equal to 8 years. However, a sensitivity analysis (see below) investigated the impact on the results of 5 years use. This was decided because, although T-Safe is licensed for 8 years, other IUDs have a 5-year licensed duration.
2. IUS: LNG-IUS (Mirena).
3. Injectable: The analysis was based on DMPA use.
4. Implant: Implanon is the only implant currently available in the UK market and therefore this form of implant was examined in the model.

The comparators of LARC methods included in the analysis were the male condom, male and female sterilisation, and the COC. Because many different brands of COC are available in the UK market, an “average” COC use was assumed (in terms of cost), based on prescription data for COC use in England, 2002[437].

8.3.5 Cost data

Cost data associated with non-reversible contraceptive methods (female and

male sterilisation) and events following contraceptive failure (live birth, miscarriage, abortion and ectopic pregnancy) were based on 2004 NHS reference costs[438], due to the lack of research-based data. Ingredient costs were derived from the British National Formulary, March 2005[121]. Regarding health service costs related to contraceptive provision, the GDG estimated that these ought to be the same regardless of the provider of contraception, i.e. Family Planning Clinics or GPs. It was decided that the estimation of health service costs would be based upon GP contraceptive provision since data on GP unit costs were available and the resource use could be estimated by the GDG. In contrast, all cost data available for Family Planning Clinics incorporated costs of providing services other than contraception, and specific costs related to contraceptive provision could not be identified. It was intended that costs reflected actual resource use rather than financial flows to GPs. Therefore, no additional fees paid to GPs for the provision of contraceptive services were considered. However, in the case of miscarriages treated in GP practices, associated costs were derived from the GP fee schedule[439] due to the lack of other resource use-based data.

Resource use with respect to contraceptive provision was based on the considered opinion of the GDG. Costs of sterile packs required at insertion and removal of some LARC methods were also based on GDG consensus. Unit costs of GP consultations for year 2004 were derived from published literature[440].

Table 8.2 shows all cost data considered in the analysis, including contraceptive method costs and costs associated with the outcomes of unintended pregnancies (i.e. continuation of pregnancy and live birth, abortion, miscarriage, and ectopic pregnancy). Contraceptive method costs are analysed in their cost components. Total method costs of each contraceptive method, consisting of ingredient and health service costs, are provided for different durations of contraceptive use (depending on method), so that comparisons between method costs of different methods are allowed.

8.3.6 Effectiveness data and other input parameters of the model

Effectiveness rates for LARC methods were derived from the results of the systematic review undertaken for the development of the guideline. Annual rates of discontinuation were based on data reported in the guideline agreed by the GDG members, or, where evidence was limited, on GDG consensus. Probabilities of ectopic pregnancy resulting from contraceptive failure were also based on data presented in the guideline. The estimation of probabilities for the other outcomes of unintended pregnancy was based on national statistics[441;442], a literature review on unintended pregnancy[430-433] and additional assumptions agreed with the GDG. Respective input data for the comparators (male condom, COC, female and male sterilisation) were derived from published literature[436;443-446]. All effectiveness data and other clinical input parameters included in the analysis are presented in Table 8.3.

Costs and outcomes occurring at a point of time longer than one year from the start of the model were discounted at an annual rate of 3.5%, as recommended by NICE guidance on Health Technology Appraisal[447].

Note: Discounting is a method of calculation by which costs and benefits of medical processes that occur at different times can be compared. The method converts the value of future costs and benefits into their present value, reflecting society's "time preference" (e.g. present benefits are valued more highly than future ones).

In order to test the robustness of the results where the variables were uncertain a sensitivity analysis was performed: alternative scenarios regarding input parameters were assumed and their impact on the base-case results was assessed. Effectiveness and discontinuation rates of LARC methods were tested by changing the base-case values by ± 10%. Additional hypotheses examined included a licensed duration of use for IUD equal to 5 years (instead of 8 years, as used in the base-case analysis), a scenario of combining LARC use with use of male condom, changes in ingredient and health service costs of the comparators (male condom, COC, female and

male sterilisation), and "perfect use" of male condom and COC (resulting in substantially lower failure rates). Finally, a sensitivity analysis by changing the discount rates was undertaken, as recommended by NICE guidance on Health Technology Appraisal[447]. Alternative input values and hypotheses tested in sensitivity analyses are reported in the respective sections of the results.

Table 8.2 Cost data included in the model

Procedure or event	Baseline value	Cost components – basic assumptions
IUD method cost First year cost: Total 5 or 8 year cost:	 £133 £159	Ingredient cost (T-Safe CU 380A): £09.56 per device[121] Initial GP consultation, 20 min: £44.80 Consultation for insertion, 18 min: £40.32 Sterile pack for insertion: £18.20 Follow-up routine consultation 3-6 weeks after insertion, 9 min: £20.16 Consultation for removal, 10 min: £22.40 Sterile pack for removal: £03.17 Resource use and cost of sterile pack based on GDG consensus; GP unit cost: £2.24 per surgery/clinic minute, including direct care staff costs and qualification costs[440]
IUS method cost First year cost: Total 5 year cost:	 £207 £232	Ingredient cost: £83.16 per device[121] Initial GP consultation, 20 min: £44.80 Consultation for insertion, 18 min: £40.32 Sterile pack for insertion: £18.20 Follow-up routine consultation 3-6 weeks after insertion, 9 min: £20.16 Consultation for removal, 10 min: £22.40 Sterile pack for removal: £03.17 Resource use and cost of sterile pack based on GDG consensus; GP unit cost: £2.24 per surgery/clinic minute[440]
Injectable method cost Annual method cost • First year: • Following years: 3 year cost: 5 year cost: 8 year cost:	 £144 £99 £342 £540 £837	Ingredient cost (DMPA): £05.01 per dose[121] Initial GP consultation (1st year), 20 min: £44.80 Consultation for injection every 12 weeks, 8 min: £17.92 Resource use based on GDG consensus; GP unit cost: £2.24 per surgery/clinic minute[440]
Implant method cost First year cost: Total 3 year cost:	 £175 £230	Ingredient cost: £90.00 per device[121] Initial GP consultation, 20 min: £44.80 Consultation for insertion, 16 min: £35.84 Sterile pack for insertion: £04.40 Consultation for removal, 22 min: £49.28 Sterile pack for removal: £05.50 Resource use and cost of sterile pack based on GDG consensus; GP unit cost: £2.24 per surgery/clinic minute[440]
Male condom method cost Annual method cost: 3 year cost: 5 year cost: 8 year cost:	 £29.00 £87.00 £145.00 £232.00	Ingredient cost: £00.56 per item (retail price) No GP consultation was considered in the calculation of method cost. It was assumed that 52 condoms were used annually, based on the results of a Welsh survey of sexual attitudes and lifestyles[448]
COC - method cost Annual method cost		Weighted, average ingredient cost: £01.37 per month[121] Initial GP consultation (1st year), 20 min: £44.80

• First year: • Following years: 3 year cost: 5 year cost: 8 year cost:	£106 £61 £228 £350 £533	Two routine consultations per year, 10 min each: £44.80 Resource use based on GDG consensus; Weighted, average price based on prescription data for COC use in England, 2002[437]; GP unit cost: £2.24 per surgery/clinic minute[440]
Female sterilisation	£712	Average NHS reference cost for Upper Genital Tract Intermediate Procedures (day-cases)[438], adding an initial 20 min GP consultation cost. In case of contraceptive failure, repeat of the procedure was considered.
Vasectomy	£455	It was estimated that 2/3 of vasectomies take place in GP practices and 1/3 in hospitals/community care settings.[435] A cost of £200 was agreed by the GDG for GP-undertaken vasectomies, including procedure and consultation costs, based on web-sources. For hospital/community-based procedures a weighted average NHS reference cost (elective, non-elective, day-cases and community-based services) was used[75] adding an initial 20 min GP consultation cost. In case of contraceptive failure, repeat of the procedure was considered.
Average contraceptive method Average annual cost: Initiation:	 £38 £45	Weighted cost based on contraceptive usage rates in England and Wales for women "at risk of pregnancy"[1]. Incidence rates rather prevalence were used for female and male sterilisation.[435] An initial 20 min GP consultation was assumed. Annual costs of male and female sterilisation were estimated by dividing total costs by 15 (average duration of effect on couple – GDG expert opinion). Additional ingredient costs for barrier methods were based on market retail prices.
Total maternity cost: Cost of antenatal care: Cost of live birth: Cost of care for unhealthy neonates + NICU for unstable neonates (adjusted per live birth)	£2137 £518 £1170 £449	NHS reference cost, including cost of antenatal care, live birth, care of unhealthy neonates and NICU levels 1 & 2[438] Costs of antenatal clinics, outpatient obstetrics and community midwifery visits were attached to the total number of births reported in the document. Weighted average of normal deliveries, assisted deliveries, and caesarean sections, treated as elective, non-elective, and day cases or in community services. Total costs of neonates that died within 2 days of birth or had one/multiple minor/major diagnoses were divided by the total number of live births reported in the document. Total costs of neonatal intensive care levels 1 & 2 were also divided by the number of live births.
Abortion	£497	Weighted average NHS reference cost (surgical or medical termination of pregnancy, treated as elective, non-elective or day case)[438]
Miscarriage	£321	Weighted average NHS reference cost 2003 (elective, non-elective and day-cases)[438] and GP fee for miscarriage 2004 (£77.50)[439]. It was assumed that 30% of miscarriages were treated by GPs (GDG expert opinion).
Ectopic pregnancy	£1,398	Weighted average NHS reference cost (elective, non-elective and day-cases) for upper genital tract intermediate procedures (reflecting laparoscopy), upper genital tract major procedures (reflecting laparotomy), and non-surgical treatment of ovaries, tube, pelvis disorders (reflecting medical treatment)[438]. The relative weights used for the estimation of costs were based on Scottish data[449]: 58% of ectopic pregnancy management involves laparoscopy, 35% involves laparotomy, and 7% of ectopic pregnancies are medically managed.

1

2

3

Table 8.3 Effectiveness rates and other clinical input parameters included in the model

Input parameter	Baseline value	Comments
Annual failure rate		
IUD		
Year 0-1:	0.500%	Annual failure rates were based on one-year and 8-year cumulative failure rates reported in the guideline. The annual failure rate between 1-8 years was assumed to be stable, as no additional data were available. After reinsertion, the annual failure rate was assumed to be equal to that between 1-8 years, as it was expected to be lower than the failure rate of the first year of first insertion.
Years 1-8:	0.246%	
Years 9-15:	0.246%	
IUS		
Year 0-5:	0.100%	Annual failure rates were based on the 5-year cumulative failure rates reported in the guideline. The annual failure rate between 0-5 years was assumed to be stable, as no additional data were available. After reinsertion, the annual failure rate was assumed to be equal to that of the first insertion.
Years 5-15:	0.100%	
Injectable		
Year 0-1:	0.100%	Annual failure rates were based on cumulative failure rates for the first two years of use reported in the guideline. It was assumed that after the second year of use, the annual failure rate was stable and equal to that of the first year of use.
Year 1-2:	0.300%	
Years 3-15:	0.100%	
Implant		
Years 1-15:	0.005%	The annual failure rate for the implant was based on GDG expert opinion. All studies included in the guideline reported no pregnancies following use of the implant.
Male condom		
Years 1-15:	15%	Failure rate for typical use, based on a published review[436]
COC		
Years 1-15:	8%	Failure rate for typical use, based on a published review[436]
Female sterilisation		
Year 0-1:	0.500%	The failure rate for the first year was based on a published review[436]. The annual failure rates for the following years are based on the cumulative 10-year rate of the CREST study reported in the RCOG guideline on sterilisation[443] after taking into account the first year's failure rate. The annual failure rate between 1-10 years was assumed to be stable over time, as no additional data were available. After 10 years the annual failure rate was assumed to be the same as year 9-10.
Years 1-10:	0.129%	
Years 10-15:	0.129%	
Vasectomy		
Year 0-1:	0.150%	The failure rate for the first year is based on a published review[436]. The annual failure rate used for the following years is that reported in the RCOG guideline on sterilisation after clearance has been given[443].
Years 1-15:	0.050%	
Average contraceptive method		
Years 1-15:	12.81%	Weighted average failure rate based on contraceptive usage rates in England and Wales for women "at risk of pregnancy"[1]

Discontinuation rates	Baseline value	Comments
IUD Year 0-1: Year 1-2: Year 2-3: Year 3-4: Year 4-5: Following years:	 21.60% 13.40% 11.80% 9.05% 5.65% 1%*	Discontinuation rates for the first 5 years of IUD use were derived from the mean values between the rates reported in a European multicentre RCT[152] and a UK community-based study, reflecting routine use[134], both reported in chapter 4. The rates refer to the initial cohort of 1000 women starting the method. *The discontinuation rate for following years was based on the GDG expert opinion and refers, each year, to the sample of women that remain in the cohort in that year, and not to the initial cohort of women.
IUS Year 0-1: Year 1-2: Year 2-3: Year 3-4: Year 4-5: Following years:	 25.25% 13.25% 8.40% 5.95% 3.90% 1%*	Discontinuation rates for the first 5 years of IUS use were derived from the mean values between the rates reported in a European multicentre RCT[152] and a UK community-based study, reflecting routine use[241], both reported in chapter 5. The rates refer to the initial cohort of 1000 women. *The discontinuation rate for following years was based on the GDG expert opinion, and refers to the sample of women that remain in the cohort each year.
Injectable Year 0-1: Following years:	 50% 5%*	The discontinuation rate for the first year of injectable use was based on the summary of evidence reported in chapter 6. *The discontinuation rate for following years was based on the GDG expert opinion, and refers to the sample of women that remain in the cohort each year.
Implant Year 0-1: Year 1-2: Year 2-3: Year 3-4 (reinsertion): Following years:	 23.55% 14.05% 9.05% 4.4% 1%*	Discontinuation rates for the first 4 years of implant use (including re-insertion) were derived from the mean values between the rates reported in an international multicentre RCT[54] and a Scottish community-based study, reflecting routine use[374], both reported in chapter 7. The rates refer to the initial cohort of 1000 women. *The discontinuation rate for following years was based on the GDG expert opinion, and refers to the sample of women that remain in the cohort each year.
Male condom	–	It was assumed that no discontinuations occurred in the cohort of women that used male condom for contraception (GDG consensus).
COC Year 0-1: Following years:	 45% 10%*	Rates based on the GDG expert opinion. *The discontinuation rate for following years refers to the sample of women that remain in the cohort each year.
Female and male sterilisation	–	For women choosing a non-reversible method (female sterilisation or vasectomy) the model assumed that no discontinuations (and subsequent reversals) occurred. In case of contraceptive failure, a repeat of the method was considered (GDG consensus).

Relative	Baseline	Comments

probability of ectopic pregnancy	value	
IUD:	6%	Based on data reported in the guideline.
IUS:	25%	Based on data reported in the guideline.
Injectable:	1.15%	For injectable, implant, male condom, COC, vasectomy and average contraceptive method, the incidence of ectopic pregnancy among pregnancies in the general population in the UK was used.[444]
Implant:	1.15%	
Male condom:	1.15%	
COC:	1.15%	
Female sterilisation:	33%	The probability used for female sterilisation was approximately equal to a calculated weighted average probability based on results reported in a cohort study[445] and consistent with the range of values reported in the RCOG guideline on sterilisation[443] and a published review[446].
Vasectomy:	1.15%	
Average contr. Method:	1.15%	
Probabilities of outcomes following unintended pregnancy (common to all methods, applied to the total number of unintended pregnancies remaining after excluding the cases of ectopic pregnancy) Live birth: Abortion: Miscarriage:	 46.4% 40.6% 13%	The probabilities used in the economic analysis account for outcomes resulting from *unintended* pregnancies. Rates of abortions and live births resulting from *all* pregnancies (both intended and unintended) are 23.4% and 76.6% respectively, based on data reported in the National Statistics for England and Wales (still births were considered negligible)[441]. No data on the number of conceptions that result in miscarriage are available for England and Wales. Data on miscarriage rates were derived from Scottish Statistics[442]. According to Scottish *hospital* data, 9% of conceptions result in miscarriage. This percentage was raised to 13% to reflect an additional number of miscarriages (around 30% of all miscarriages) treated in GP practices (GDG expert opinion). After the number of conceptions that led to miscarriage was estimated, the probabilities of outcomes of *all* conceptions (both intended and unintended) in England and Wales were as follows: abortions 20.3%, live births 66.7%, and miscarriages 13%. Abortions were assumed to derive from *unintended* pregnancies only, as therapeutic abortions accounted for less than 1% and therefore were considered negligible. The probability of miscarriage is not affected by intention of becoming pregnant, so it is still 13% in the case of unintended pregnancies. It was assumed that 50% of conceptions reported in England and Wales in 2001 were unintended, this assumption being consistent with estimates from other studies[427;431-433]. Consequently, abortions account for 40.6% (20.3% x 2) of *unintended* pregnancies, which is in agreement with the findings of published studies[432;434]. The remaining 46.4% of *unintended* pregnancies represents live births.
Discount rate	3.5%	Recommended by NICE guidance on Health Technology Appraisal[121], applied both to costs and benefits.

8.4 Results of the economic analysis

The results of the economic analysis are presented in the form of incremental cost-effectiveness ratios (ICERs), expressing 'additional cost per additional pregnancy averted' of one method compared with another. The estimation of this ratio allows for direct comparison between different contraceptive methods, assessing whether the additional benefit (pregnancies averted) is worth the additional cost when switching from one method to another.

$$\text{ICER} = \frac{\text{Difference in costs}}{\text{Difference in benefits}} \text{ between methods}$$

$$= \frac{\text{Additional cost}}{\text{Additional pregnancies averted}} \text{ of one method versus another}$$

In the case of one method being more effective and less costly than its comparator (defined as the "dominant option"), the calculation of such a ratio is not required. More effective in this context means that the method is associated with a lower number of pregnancies *after discontinuation has been taken into account*, and not simply that the method's clinical effectiveness, expressed by the contraceptive failure rate, is higher than that of the comparator.

Results of the base-case scenario are presented first. This scenario is based on the most accurate estimates available, with respect to both effectiveness and cost data used in the model. The base-case analysis is followed by the results of sensitivity analysis, in which the impact of alternative hypotheses regarding input parameters on the base-case results was investigated. Results of sensitivity analysis are not fully reported unless the assumptions used have an impact on the relative-cost effectiveness of LARC methods.

Conclusions on relative cost-effectiveness have been drawn on the basis of dominance of one contraceptive method over its comparator. In the case of one method being both more effective and more costly than its comparator, then no clear conclusion on relative cost-effectiveness could be drawn. The GDG did not feel empowered to attach a value on unintended pregnancy averted by contraceptive use, expressed in monetary terms. Consequently, it could not determine a cost-effectiveness threshold that would allow clear statements on cost-effectiveness to be made, based on the ICERs reported in this guideline.

The value of averting an unintended pregnancy is very difficult to estimate. The financial cost of an unintended pregnancy (cost-saving in case of preventing such an event) has already been included at the estimation of total costs associated with a contraceptive method; using this cost as a proxy for valuing an unintended pregnancy averted would lead to double counting of respective costs. Moreover, in order to estimate this value, one needs to consider the psychological distress to the woman and her family following an unintended pregnancy, the value of a life forgone due to contraceptive use (or of a life resulting from contraceptive failure), and also the long-term costs and benefits (both financial and intangible) to the society associated with an unintended pregnancy (either occurring or averted). Currently, there are no research data to indicate what the society is willing to pay in order to prevent an unintended pregnancy. Therefore, although ideally a cost-effectiveness threshold should be determined expressing the point above that an additional benefit (unintended pregnancy averted) is not worth the additional cost incurred- this was not feasible in the context of this guideline; the lack of establishing an absolute cost-effectiveness threshold is acknowledged as a limitation of the analysis.

Note 1: In some scenarios involving the IUD, the IUS and the implant, results are notably affected by the time frame of the analysis. This is caused to some extent by the time-dependency of the respective method costs: (re-)insertion of the above devices is associated with additional healthcare resource use and therefore incurs additional costs in the year in which it occurs. For periods

of use ending soon after (re-)insertion, total costs associated with the above methods are relatively high; these costs decrease as the period of use approaches the full licensed duration of each LARC device, because the high costs of (re-)insertion are spread over longer periods of time.

Note 2: In some cases the ICERs reported are shown to be relatively high. This is explained by the fact that, in general, all forms of contraception examined are highly effective (this also applies to the male condom and COC when perfect use is achieved); therefore the difference in benefit between methods (the additional number of pregnancies averted) is very small. The difference in associated costs (the additional cost) may also be small (but not *as* small). Therefore, a small additional cost is divided by a *very* small additional number of pregnancies averted, resulting in a relatively large ICER.

8.4.1 Base-case analysis

Results from all comparisons considered in the analysis are presented in table 8.4, for all time frames examined, starting from 1 and up to 15 years of contraceptive use. For each time frame all contraceptive methods are ranked from the most to the least effective. Cases of absolute dominance and extended dominance are demonstrated (extended dominance of a method occurs where the ICER between this method and the subsequent more effective one is higher than the ICER between the preceding more effective method and the method in question). However, all ICERs resulting from comparisons where one method is more costly and more effective than another are presented for reasons of clarity.

Table 8.4 Total costs and pregnancies per 1000 women from one to fifteen years of contraceptive use

1 year of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	2	457,538	Male sterilisation vs implant: £14,230/pregnancy averted Male sterilisation vs IUS: £12,015/pregnancy averted Male sterilisation vs IUD: £15,606/pregnancy averted Male sterilisation vs injectable: £8,537/pregnancy averted
Female sterilisation	5	722,004	Female sterilisation vs implant: £45,260/pregnancy averted Female sterilisation vs IUS: £37,460/pregnancy averted Female sterilisation vs IUD: £39,607/pregnancy averted Female sterilisation vs injectable: £19,135/pregnancy averted
Implant	15	263,613	**Implant vs IUD: £21,526/pregnancy averted** Implant vs injectable: £4,141/pregnancy averted
IUS	17	270,749	**Dominated by implant** IUS vs IUD: £60,322/pregnancy averted IUS vs injectable: £5,100/pregnancy averted
IUD	18	195,442	**IUD vs injectable: £339/pregnancy averted**
Injectable	33	190,534	
COC	91	232,932	**Dominated by IUD and injectable** Implant vs COC: £405/pregnancy averted IUS vs COC: £513/pregnancy averted
Condom	150	212,658	**Dominated by IUD and injectable** Implant vs condom: £378/pregnancy averted IUS vs condom: £437/pregnancy averted

2 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	2	458,355	Male sterilisation vs implant: £2,598/pregnancy averted Male sterilisation vs IUD: £3,804/pregnancy averted Male sterilisation vs IUS: £2,198/pregnancy averted Male sterilisation vs injectable: £1,235/pregnancy averted
Female sterilisation	6	724,498	Female sterilisation vs implant: £8,527/pregnancy averted Female sterilisation vs IUD: £9,593/pregnancy averted Female sterilisation vs IUS: £7,610/pregnancy averted Female sterilisation vs injectable: £4,157/pregnancy averted
Implant	53	325,806	**Implant vs IUD: £34,243/pregnancy averted**
IUD	55	256,572	
IUS	57	337,093	**Dominated by implant, IUD**
Injectable	99	338,376	**Dominated by implant, IUD, IUS**
COC	190	406,366	**Dominated by all LARC methods**
Condom	295	418,125	**Dominated by all LARC methods**

1

3 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	2	459,145	**Dominates injectable** Male sterilisation vs implant: £529/pregnancy averted Male sterilisation vs IUD: £1,186/pregnancy averted Male sterilisation vs IUS: £381/pregnancy averted
Female sterilisation	7	726,907	Female sterilisation vs implant: £3,339/pregnancy averted Female sterilisation vs IUD: £3,983/pregnancy averted Female sterilisation vs IUS: £3,043/pregnancy averted Female sterilisation vs injectable: £1,537/pregnancy averted
Implant	104	405,577	**Implant vs IUD: £42,252/pregnancy averted**
IUD	105	337,207	
IUS	109	418,616	**Dominated by implant, IUD**
Injectable	167	482,178	**Dominated by implant, IUD, IUS**
COC	289	575,320	**Dominated by all LARC methods**
Condom	435	616,644	**Dominated by all LARC methods**

2

3

4 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	3	459,908	**Dominates implant, IUS, injectable** Male sterilisation vs IUD: £171/pregnancy averted
Female sterilisation	9	729,235	Female sterilisation vs implant: £953/pregnancy averted Female sterilisation vs IUD: £1,892/pregnancy averted Female sterilisation vs IUS: £1,393/pregnancy averted Female sterilisation vs injectable: £471/pregnancy averted
Implant	161	584,349	**Implant vs IUD: £30,375/pregnancy averted** Implant vs IUS: £12,229/pregnancy averted
IUD	166	432,018	
IUS	167	508,869	**Dominated by IUD**
Injectable	234	622,935	**Dominated by implant, IUD, IUS**
COC	386	739,765	**Dominated by all LARC methods**
Condom	570	808,450	**Dominated by all LARC methods**

4

5

5 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	3	460,645	**Dominates all LARC methods**	
Female sterilisation	10	731,485	**Dominates injectable** Female sterilization vs implant: £284/pregnancy averted Female sterilization vs IUS: £585/pregnancy averted Female sterilization vs IUD: £886/pregnancy averted	
Implant	219	672,035	Implant vs IUS: £7,083	**Implant vs IUD: £10,312/pregnancy averted**
IUS	228	603,534	IUS vs IUD: £18,845/pregnancy averted	**Extended dominance**
IUD	232	534,555		

Injectable	302	760,600	**Dominated by implant, IUD, IUS**
COC	482	899,697	**Dominated by all LARC methods**
Condom	701	993,769	**Dominated by all LARC methods**

1

2

6 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	4	461,358	**Dominates all LARC methods**
Female sterilisation	11	733,658	**Dominates implant, IUS, injectable** Female sterilization vs IUD: £336/pregnancy averted
Implant	276	757,841	**Implant vs IUD: £5,089/pregnancy averted**
IUS	290	767,736	**Dominated by implant** IUS vs IUD: £14,226/pregnancy averted
IUD	299	636,652	
Injectable	370	895,141	**Dominated by implant, IUD, IUS**
COC	576	1,055,131	**Dominated by all LARC methods**
Condom	827	1,172,822	**Dominated by all LARC methods**

3

4

7 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	4	462,046	**Dominates all LARC methods**	
Female sterilisation	12	735,758	**Dominates all LARC methods**	
Implant	331	914,756	Implant vs IUS: £2,872/pregnancy averted	**Implant vs IUD:** **£5,271/pregnancy averted**
IUS	351	859,181	IUS vs IUD: £8,459/pregnancy averted	**Extended dominance**
IUD	365	736,023		
Injectable	437	1,026,537	**Dominated by implant, IUD, IUS**	
COC	668	1,206,102	**Dominated by all LARC methods**	
Condom	949	1,345,820	**Dominated by all LARC methods**	

5

6

8 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	5	462,711	**Dominates all LARC methods**	
Female sterilisation	13	737,786	**Dominates all LARC methods**	
Implant	385	996,365	Implant vs IUS: £2,015/pregnancy averted	**Implant vs IUD:** **£3,756/pregnancy averted**
IUS	409	948,186	IUS vs IUD: £5,871/pregnancy averted	**Extended dominance**

IUD	429	832,635	
Injectable	504	1,154,780	**Dominated by implant, IUD, IUS**
COC	758	1,352,655	**Dominated by all LARC methods**
Condom	1067	1,512,967	**Dominated by all LARC methods**

1

2

9 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	5	463,353	**Dominates all LARC methods**	
Female sterilisation	14	739,747	**Dominates all LARC methods**	
Implant	438	1,075,916	Implant vs IUS: £1,455/pregnancy averted	**Implant vs IUD: £2,216/pregnancy averted**
IUS	466	1,034,800	IUS vs IUD: £3,091/pregnancy averted	**Extended dominance**
IUD	491	958,830		
Injectable	570	1,279,871	**Dominated by implant, IUD, IUS**	
COC	846	1,494,852	**Dominated by all LARC methods**	
Condom	1181	1,674,462	**Dominated by all LARC methods**	

3

4

10 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	5	463,974	**Dominates all LARC methods**
Female sterilisation	15	741,640	**Dominates all LARC methods**
Implant	490	1,217,464	**Implant vs IUS: £3,033/pregnancy averted** Implant vs IUD: £2,707/pregnancy averted
IUS	522	1,119,079	**IUS vs IUD: £2,346/pregnancy averted**
IUD	551	1,050,425	
Injectable	635	1,401,818	**Dominated by implant, IUD, IUS**
COC	932	1,632,762	**Dominated by all LARC methods**
Condom	1,291	1,830,496	**Dominated by all LARC methods**

5

6

11 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	6	464,574	**Dominates all LARC methods**	
Female sterilisation	16	743,470	**Dominates all LARC methods**	
Implant	540	1,293,020	Implant vs IUS: £990/pregnancy averted	**Implant vs IUD: £2,192/pregnancy averted**

IUS	576	1,256,971	IUS vs IUD: £3,489/pregnancy averted	**Extended dominance**
IUD	610	1,139,234		
Injectable	700	1,520,639	**Dominated by implant, IUD, IUS**	
COC	1,016	1,766,460	**Dominated by all LARC methods**	
Condom	1,397	1,981,254	**Dominated by all LARC methods**	

1

2

12 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	6	465,153	**Dominates all LARC methods**	
Female sterilisation	17	745,238	**Dominates all LARC methods**	
Implant	588	1,366,633	Implant vs IUS: £741/pregnancy averted	**Implant vs IUD: £1,803/pregnancy averted**
IUS	629	1,336,833	IUS vs IUD: £2,928/pregnancy averted	**Extended dominance**
IUD	667	1,225,501		
Injectable	764	1,636,357	**Dominated by implant, IUD, IUS**	
COC	1,098	1,896,031	**Dominated by all LARC methods**	
Condom	1,500	2,126,913	**Dominated by all LARC methods**	

3

4

13 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios	
Male sterilisation	6	465,713	**Dominates all LARC methods**	
Female sterilisation	17	746,946	**Dominates all LARC methods**	
Implant	636	1,494,323	Implant vs IUS: £1,818/pregnancy averted	**Implant vs IUD: £2,151/pregnancy averted**
IUS	680	1,414,530	IUS vs IUD: £2,498/pregnancy averted	**Extended dominance**
IUD	722	1,309,296		
Injectable	826	1,749,003	**Dominated by implant, IUD, IUS**	
COC	1,177	2,021,563	**Dominated by all LARC methods**	
Condom	1,600	2,267,647	**Dominated by all LARC methods**	

5

6

14 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Male sterilisation	7	466,254	**Dominates all LARC methods**
Female sterilisation	18	748,596	**Dominates all LARC methods**

Implant	682	1,564,174	Implant vs IUS: £1,564/pregnancy averted	**Implant vs IUD: £1,857/pregnancy averted**
IUS	730	1,490,079	IUS vs IUD: £2,159/pregnancy averted	**Extended dominance**
IUD	776	1,390,690		
Injectable	888	1,858,611	**Dominated by implant, IUD, IUS**	
COC	1,255	2,143,148	**Dominated by all LARC methods**	
Condom	1,695	2,403,622	**Dominated by all LARC methods**	

15 years of use	**Total pregnancies**	**Total costs (£)**	**Incremental Cost-effectiveness Ratios**	
Male sterilisation	7	466,776	**Dominates all LARC methods**	
Female sterilisation	19	750,191	**Dominates all LARC methods**	
Implant	727	1,632,199	Implant vs IUS: £1,354/pregnancy averted	**Implant vs IUD: £1,617/pregnancy averted**
IUS	778	1,563,548	IUS vs IUD: £1,884/pregnancy averted	**Extended dominance**
IUD	828	1,469,754		
Injectable	948	1,965,220	**Dominated by implant, IUD, IUS**	
COC	1,330	2,260,880	**Dominated by all LARC methods**	
Condom	1,788	2,534,998	**Dominated by all LARC methods**	

8.4.1.1 Comparison of LARC methods with other reversible contraceptive methods (male condom and COC)

All LARC methods are associated with a smaller number of pregnancies compared to the male condom and the COC across all time periods examined. For one year of use, the IUD and the injectable dominate the male condom as well as the COC (i.e. IUD and the injectable are less costly and more effective than male condom and COC). The implant is more effective and more costly than the male condom and the COC for one year of use, incurring an additional cost equal to £378 and £405 per pregnancy averted, respectively. For the same time-frame, the IUS is also more effective and more costly than the male condom and the COC, at an additional cost of £437 and £513 per pregnancy averted, respectively.

For periods of contraceptive use equal to 2 years and above, all LARC methods dominate the male condom and the COC.

Evidence statement

LARC methods are more cost-effective compared to the male condom and the COC, even for short periods of contraceptive use (1-2 years).

8.4.1.2 Comparison of LARC methods with non-reversible contraceptive methods (male and female sterilisation)

Both female and male sterilisation are more effective than all LARC methods across all time frames examined. This is explained by the high discontinuation rates of LARC that lead to the use of less effective contraceptive methods (summarised in the concept of average contraceptive method, as described).

Female sterilisation is more costly than any LARC method for periods of use up to 4 years, incurring high incremental costs per pregnancy averted that reach £45,260 (versus the implant) for one year of use. However, these incremental costs decrease as the duration of contraceptive use increases (with all ICERs becoming lower than £2,000 per pregnancy averted at 4 years of use), until female sterilisation becomes the dominant option; this happens at 5 years of use when it is compared to the injectable, at 6 years of use when the comparator is the IUS or the implant, and at 7 years of use compared to the IUD. For duration of contraceptive use equal to 7 years and above (up to 15 years examined), female sterilisation dominates all LARC methods.

Male sterilisation is more costly than any LARC method for periods of contraceptive use up to 2 years. The ICERs between male sterilisation and LARC methods are lower than the respective ICERs of female sterilisation, when the same periods of use are examined. The highest ICER of male sterilisation is that resulting from comparison with IUD for one year of use, equalling £15,606 per pregnancy averted, which falls at £3,804 at 2 years of use (all other ICERs are lower than £2,600 at 2 years of use). Male sterilisation dominates the injectable at 3 years of use, the IUS and the

implant at 4 years of use, and the IUD at 5 years of use. The dominance of male sterilisation over LARC methods persists thereafter, as expected, up to the maximum time frame examined (15 years).

Evidence statement

Female sterilisation is more cost-effective than all LARC methods for long periods of contraceptive use, starting from 5 years (compared to the injectable), 6 years (compared to the IUS and the implant) or 7 years (compared to the IUD) and above.

Male sterilisation is more cost-effective than LARC methods for periods of contraceptive use starting from 3 years (compared to the injectable), 4 years (compared to the IUS and the implant), or 5 years (compared to the IUD) and above.

8.4.1.3 Comparisons between LARC methods

The injectable is dominated (is more costly and prevents a lower number of pregnancies) by all other LARC methods, i.e. the IUD, the IUS and the implant, for periods of use starting from 2 and up to 15 years. For one year of use, the injectable is the cheapest but also the least effective among LARC methods; the ICERs of the IUS, the implant and the IUD compared to the injectable for one year of use are £5,100, £4,141 and £339 per pregnancy averted respectively.

The IUS is dominated by the *IUD* for 2 and up to 4 years of use. For longer periods and up to the maximum 15-year time horizon examined, the IUS is more effective than the IUD, but at an additional cost. The ICER of IUS compared to IUD generally tends to decrease overtime, although a small increase is observed at 11 years of use, due to costs of IUS re-insertion after 10 years of use. The additional cost of IUS compared to IUD starts from £18,845 per pregnancy averted for 5 years of use, and falls to £1,884 per pregnancy averted at 15 years of use. For one year of use, the IUS is also

more effective and more costly than the IUD, with an ICER of £60,322 per pregnancy averted.

The IUS is dominated by the implant for short periods of use, up to 3 years, and also for 6 years of use. For the other time-frames examined, the implant is both more effective and more costly than the IUS, with ICERs ranging between £12,229 per pregnancy averted at 4 years of use and £741 per pregnancy averted at 12 years of use, depending also on the times of re-insertion of the two methods. For periods of use equalling 5 years and above, with the exception of 6 and 10 years of use, the IUS is dominated by the implant according to the rule of extended dominance. This means that the ICER between the implant and the IUS is lower than that between the IUS and the IUD (which is the next most effective method in ranking).

The implant is the most effective among LARC methods. For short periods of use up to 4 years, its ICER compared to the *IUD* ranges from £21,526 (one year of use) to £42,252 (3 years of use) per pregnancy averted. This ratio falls to £10,312 per pregnancy averted at 5 years of use, and decreases thereafter, reaching a cost of £1,617 per pregnancy averted at 15 years of use, with slight increases at 10 and 13 years of use, due to implant re-insertion costs.

Evidence statement

The implant is more cost-effective than the IUS for periods of use between 1 and 3 years, and also for 6 years of use. It is also more cost-effective than the injectable for contraceptive use equal to 2 years and above.

The IUD is more cost-effective than IUS for periods of use between 2 and 4 years. It is also more cost-effective than the injectable for 2 and up to 15 years of contraceptive use.

IUS is more cost-effective than the injectable between 2 and 15 years of contraceptive use. IUS is less cost-effective than the implant for all time-frames examined (according to simple or extended dominance), with the

exception of 4 years of use. It is also less cost-effective than IUD for periods of use between 2-4 years.

The injectable is less cost-effective than any other LARC method for any duration of contraceptive use equal to 2 years and above.

8.4.2 Sensitivity analysis

8.4.2.1 Varying the failure rates of all contraceptive methods included in the analysis

Varying the failure rates of male condom and COC by ± 10%

Varying the failure rates of male condom and COC by ± 10% does not affect the base-case results.

Varying the failure rates of male and female sterilization by ± 10%

Varying the failure rates of male and female sterilisation by ± 10% does not have any impact on the base-case results of the analysis.

Varying the failure rates of LARC methods by ± 10%

Varying the failure rates of LARC methods by ± 10% does not have any impact on their relative cost-effectiveness compared to all other reversible and non-reversible contraceptive methods included in the analysis. In addition, it does not affect ranking of LARC methods in terms of effectiveness, or cases of dominance and extended dominance resulting from comparisons within LARC methods. The ICERs between LARC methods are not affected by changes in failure rates of the implant, the IUS and the injectable by ± 10%. However, varying the failure rate of IUD has a significant impact on the ICERs between this and the other LARC methods for short periods of contraceptive use, up to 5-6 years. For longer periods of use the relative cost-effectiveness between LARC is totally unaffected by changes in their failure rates. The

range of ICERs between IUD and the other LARC methods estimated after changing the failure rates of IUD by ± 10% are presented in Appendix C.

Evidence statement

The relative cost-effectiveness of LARC methods compared to other reversible and non-reversible contraceptive methods is robust to small changes in failure rates. The relative cost-effectiveness between LARC methods is also rather insensitive to small changes in failure rates in general, especially in the long run.

8.4.2.2 Varying the discontinuation rates of LARC methods / COC

Decreasing or increasing discontinuation rates of LARC methods by ± 10% does not change their relative cost-effectiveness compared to male condom and COC for all time horizons considered. Base-case results are also robust to ± 10% changes in the discontinuation rate of COC.

The cost-effectiveness of LARC compared to male and female sterilisation is modestly sensitive to changes in LARC discontinuation rates for short periods of use. Results involving comparisons of LARC methods to male sterilisation are only slightly affected with respect to ICERs; cases of dominance remain the same as those reported for the base-case scenario. Regarding comparison with female sterilisation, increasing the discontinuation rates of all LARC methods by 10% does not affect the cases of dominance as well, but has a stronger impact on the ICERs, especially for short periods of use equal to 1-2 years. More significantly, besides changes in ICERs, decreasing the discontinuation rates of LARC methods by 10% also changes the time over which female sterilisation becomes the dominant option: although dominance over the injectable still occurs at 5 years of use, female sterilisation dominates the IUS and the implant at 7 years of use (instead of 6) and the IUD at 8 years of use (instead of 7).

The results of the comparisons between LARC and non-reversible methods under this scenario are presented in Appendix C, referring to periods of contraceptive use up to 5 years for male sterilisation and 8 years for female sterilisation, as at this time non-reversible methods become dominant options over all other LARC methods under this scenario, and no further changes in the results occur.

The relative cost-effectiveness between LARC methods is substantially affected by altering the LARC discontinuation rates between ± 10% of the base-case values. The only exception is the injectable, the relative cost-effectiveness of which is rather insensitive to these changes: results involving comparisons of injectable with other LARC methods remain the same, and only a 10% increase in IUS or a 10% decrease in injectable discontinuation rates delays the dominance of IUS over the injectable by one year, compared to the base-case analysis (under this scenario it starts at 3 instead of 2 years).

Regarding relative cost-effectiveness between the implant and IUS, when implant discontinuation rates increase by 10% or IUS discontinuation rates decrease by the same percentage, then IUS becomes constantly more effective and dominates the implant for most periods of use examined. In contrast, after a change of –10% in implant or +10% in IUS discontinuation rates, the implant becomes the dominant option across several time horizons.

In the case of comparisons between IUD and IUS, applying a 10% increase in IUD or a 10% decrease in IUS discontinuation rates, results in IUS being constantly more effective than IUD. This means that IUD does not dominate IUS over 2-4 years of use; on the contrary, IUS dominates IUD at 10 and 15 years of use (and 14 years, when IUD discontinuation rates increase). Dropping IUD or raising IUS discontinuation rates by 10%, on the other hand, makes IUD the dominant method over all time periods examined.

Finally, with regard to comparisons between the implant and IUD, a 10% rise in implant or a 10% fall in IUD discontinuation rates leads to IUD becoming dominant at 2-6 years of use (and also at 7 years, when IUD discontinuation

rates decrease); for the other time frames examined, the implant remains more effective and more costly than IUD. Changing the discontinuation rates by –10% for the implant and +10% for IUD causes only a reduction in ICERs of the implant versus IUD; the implant remains more effective and more costly than IUD across all time periods examined, as is the case in the base-case scenario.

The results under this scenario from comparisons between IUS, IUD and the implant are provided in Appendix C.

Evidence statement

The relative cost-effectiveness of LARC methods compared to male condom and COC is not sensitive to small changes in discontinuation rates.

The cost-effectiveness of LARC methods compared to male and female sterilisation is modestly affected by small changes in LARC discontinuation rates for short periods of contraceptive use.

Discontinuation is an important driver of relative cost-effectiveness between LARC methods, with the exception of the injectable; even small changes in discontinuation rates cause significant differences in relative cost-effectiveness between IUS, IUD, and the implant.

8.4.2.3 Applying a 5-year licensed duration of use for IUD

This scenario was considered as some IUDs are only licensed for 5 years of use, and therefore removal of the device and re-insertion needs to take place twice, at the end of 5 and 10 years (for longer time frames examined), and not only once, at the end of 8 years, with the 8-year licensed IUD used in the base-case analysis. A sensitivity analysis investigated whether this difference in resource use and associated costs has any impact on the cost-effectiveness of IUD compared to other contraceptive methods.

Results are not sensitive to such a hypothesis. The ICERs of implant and IUS compared to IUD are slightly affected (between 6 and 15 years of use), but this is the only effect on the base-case results. A shorter duration of use has no impact on relative cost-effectiveness between IUD and the rest contraceptive methods assessed, either reversible or not.

Evidence statement

The cost-effectiveness of IUD is similar either for a 5- or an 8-year licensed duration of use.

8.4.2.4 LARC methods combined with male condom versus male condom alone

A sensitivity analysis was undertaken to compare the combination of LARC methods *plus* male condom versus male condom alone. This was considered appropriate, as many condom users are likely to be at high-risk for STIs, and therefore select this method not only for purposes of contraception, but also for protection against STIs. Consequently, a meaningful comparison should incorporate this parameter (protection against STIs) in both interventions assessed.

Failure rates of the combination of every LARC method with male condom were assumed to be those of the LARC method alone (additional contraceptive protection of male condom was thought to be negligible), and, as a result, failure costs (associated with outcomes of unintended pregnancy) were also equal to those related to the LARC method alone. Method costs of the combination were the sum of LARC method costs plus the male condom method costs. Discontinuation rates were assumed to be those of LARC alone.

The results were only slightly sensitive to this scenario. For one year of contraceptive use, the ICERs of the implant/male condom and the IUS/male condom compared with male condom alone become £567 and £627 per pregnancy averted, respectively, while the IUD/male condom is more costly

than male condom alone, with an ICER of £65 per pregnancy averted. The injectable/male condom dominates the male condom alone for one year of use. For periods of use of 2 years and up to 15 years examined, all LARC method combinations with male condom dominate the male condom alone.

Evidence statement

LARC methods combined with male condom are most cost-effective compared to male condom alone for 1-2 years of use and above.

8.4.2.5 Varying the method costs of the comparators

Changes in the cost and number of condoms used per year

The annual use of 52 condoms at a cost of 56p each, used in the base-case scenario, is a rather conservative assumption. A sensitivity analysis using a price per item of 19p (a price at which primary care practices are likely to buy condoms in bulk, as suggested by the GDG) does not change the results substantially, in both the base-case scenario and the alternative scenario of LARC methods combined with male condom. For one year of use, the IUD becomes only slightly more costly than male condom, with an ICER at £5 per pregnancy averted (the injectable remains a dominant option); similarly, the combination of injectable/male condom becomes slightly more costly than male condom alone, with an ICER at £26 per pregnancy averted. The other ICERs (of LARC alone or combined to male condom versus male condom alone) remain at the same levels, ranging from £72 (IUD/male condom) to £636 (IUS/male condom). All LARC methods (alone or combined with male condom) become the dominant options after one year of use and longer. Increasing the number of condoms used per year or the ingredient cost would only favour LARC methods further.

Changes in the ingredient cost, duration or frequency of follow-up consultations of COC

Using the lowest ingredient cost for COC[121], assuming a shorter follow-up

consultation time of 5 min (instead of 10) every six months for COC or one (instead of 2) follow-up consultation of 10 min annually, or combining scenarios for ingredient cost and consultation times, does not have any strong impact on the results; it affects only the ICER values of the IUS and the implant versus the COC at one year of use (they become £836 and £721 per pregnancy averted, respectively, when the two scenarios are combined). The cases of dominance remain the same as those of the base-case scenario.

Changes in procedure costs of female and male sterilisation

20% increase in sterilisation costs: Base-case results are moderately affected by this scenario, regarding short periods of use. Female sterilisation becomes dominant over all LARC methods at 9 years of use, whereas the same applies to male sterilisation at 5 years of use.

20% decrease in sterilisation costs: In this case female sterilisation dominates any LARC method for periods of contraceptive use starting from 6 years and above. Male sterilisation dominates any LARC method at 4 years of use.

Evidence statement

Relative cost-effectiveness between LARC methods and male condom is not sensitive to changes in the ingredient cost of male condom or the number of items used annually.

Relative cost-effectiveness between LARC and COC is not practically affected by changes in ingredient cost and/or the duration and frequency of follow-up consultations of COC.

The relative cost-effectiveness between sterilisation (both female and male) and LARC methods is relatively sensitive to 20% changes in sterilisation costs, but only in the short term.

8.4.2.6 Perfect use of male condom and COC

Perfect use of male condom

Under this scenario the perfect use of male condom was assumed, characterised by an annual failure rate equal to 2%, as reported in a published review[436]. The male condom dominates all LARC methods, used alone or in combination to male condom, after one year of use. In addition, it dominates the injectable for one year of use. The other LARC methods, combined with male condom or alone, are slightly more effective than the perfect use of male condom at one year of use, but at a substantially higher cost (resulting in a range of ICERs between £43,128 and £98,339 per pregnancy averted).

These results are explained by the high discontinuation rates of LARC methods, which leads to the use of the average contraceptive method, which is far less effective than the perfect use of male condom (failure rates 12.84% versus 2% respectively). In contrast, no discontinuation was assumed with respect to the male condom. Results for one and up to 4 years of use are shown in Appendix C.

Perfect use of COC

Perfect use of COC is characterised by an annual failure rate equal to 0.3%, as reported in a published review[436]. Results remain relatively robust regarding IUD and IUS when perfect use of COC is assumed. IUD dominates COC for time frames starting from 2 years of use and above, while the dominance of IUS over COC starts at 4 years of use. The implant remains more effective, but it is also more costly for short periods of use (up to 5 years), with the exception of 3 years of use, where implant dominates the COC. The ICER of the implant compared to COC for the above periods ranges from £6,548 per pregnancy averted (for one year of use) to £86 per pregnancy averted (for 5 years of use). For periods of use equal to 6 years and above, the implant dominates COC. When COC is perfectly used, it dominates the injectable for periods of use up to 6 years. After this time, the

injectable becomes more effective for the rest of the time horizons examined, with an ICER that constantly decreases, having its highest value for 7 years of use, at £58,242 per pregnancy averted, and its lowest for 15 years of use, at £1,507 per pregnancy averted.

The above results are not as favourable for perfect use of COC as for perfect use of male condom. This is explained by the high discontinuation rates characterising the use of COC, that reduce its overall effectiveness despite its perfect use (for male condom no discontinuation was assumed). Full results of this scenario are also presented in Appendix C.

Evidence statement

Male condom is more cost-effective than LARC methods (used alone or in combination with male condom) starting from 1-2 years of use, when perfect use of it is achieved, due to high discontinuation rates characterising LARC methods.

IUD and IUS are more cost-effective than COC, even when perfect use of COC is achieved, for periods of contraceptive use starting from 2 and 4 years respectively and above. The implant is more cost-effective than perfect use of COC for durations of use equal to 6 years and above, and also at 3 years of use, where the total licensed duration of implant use is exploited. Perfect use of COC becomes more cost-effective than the injectable for shorter periods of contraceptive use, up to 6 years.

8.4.2.7 Varying discount rates between 0-6%

This scenario was investigated as recommended by NICE guidance on Health Technology Appraisal[447]. All base-case results are rather insensitive to changes in discount rate. Relative cost-effectiveness between LARC methods and female sterilisation is the most sensitive for short periods of use (up to 6-7 years), but the changes are not significant.

8.5 Limitations of the economic analysis – further considerations

The economic analysis was based on the best evidence available. The validity of the results is higher when shorter time frames are considered, as in this case effectiveness and discontinuation rates were based on available data reported in the guideline and not on assumptions. However, results on relative cost-effectiveness between LARC methods were found to be highly sensitive to changes in discontinuation rates and therefore, in many cases, a rigorous interpretation of the results was not allowed.

The decision-analytic model incorporated events such as contraceptive failure leading to unintended pregnancy and discontinuation. The latter was demonstrated to be a significant determinant of the relative cost-effectiveness between LARC methods. However, other events associated with contraceptive use were not reflected in the results. Use of LARC methods is often followed by side effects. Besides causing distress to the user, some side-effects may require additional healthcare resource use for their management (e.g. hospitalisation), which has not been considered in the model; this is acknowledged as a limitation of the analysis. Nevertheless, the frequency of side-effects related to LARC use is partially reflected in rates of discontinuation (since a proportion of discontinuations is caused due to side effects), and the possibility and consequences of such an event (subsequent use of a less effective method and increased risk of contraceptive failure) was included in the model design.

In addition, other non-contraceptive benefits, such as the management of menstrual disorders achieved with IUS use and the protective role of male condom against STIs, were not considered in the analysis. In the case of IUS, including such a beneficial effect might substantially affect the method's relative cost-effectiveness compared to other LARC methods. Regarding the omission of the protective role of male condom against STIs from the model structure, a sensitivity analysis evaluated the cost-effectiveness of LARC methods combined with male condom versus male condom alone; in this case, both comparators provided protection against STIs, and the limitation of

not taking into account this non-contraceptive benefit associated with use of condom was overcome; as in the base-case analysis, LARC methods (used together with male condom) proved to be more cost-effective than male condom.

Psychological factors, such as the satisfaction and quality of life coming from contraceptive use, or the distress to the woman and her family following an unintended pregnancy, the value of a life forgone due to contraceptive use or a life resulting from a contraceptive failure, were also not taken into account in the economic analysis.

The analysis included comparisons of LARC methods with non-reversible contraception (male and female sterilisation). However, the latter cannot always be considered an alternative to LARC use. Comparison of LARC methods with male sterilisation presupposes the couple an “unit of protection” and not the woman alone. Female sterilisation is not a realistic option for women who may wish to retain their fertility. Furthermore, it has been reported that 10% of couples that have chosen sterilisation as their method of contraception regret this decision at a later date, while only 1% of them undergo a reversal procedure[450]. In all these cases, use of LARC methods can be regarded as a relevant contraceptive option.

Users’ compliance is an important issue that has to be taken into account in the interpretation of the results. Perfect use of COC (which has been demonstrated to be more cost-effective compared to some LARC methods and for some durations of use) requires perfect compliance with the method. This is not the case in particular for certain sub-groups of the population, such as adolescents [451] or women with no established regular routine[452]. The use of LARC methods in this case is more cost-effective, since their effectiveness in practice does not depend on users’ compliance.

In conclusion, cost-effectiveness of LARC methods is only one factor to consider when making choices about contraception. At an individual level, women’s’ preferences, acceptability, individual needs and lifestyle should

determine the final decision on the contraceptive method to be used.

9 Auditable standards

Table 9.1 Suggested audit criteria

Criterion	Exceptions	Definitions of terms
Women requiring contraception should be provided with information and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. [D/GPP]		
Women considering LARC methods should receive both verbal and written information that will enable them to choose and use the method effectively. This information should take into consideration their individual needs and should include: • contraceptive efficacy • risks and possible side effects • advantages and disadvantages • non-contraceptive benefits • the procedure for initiation and removal/discontinuation • duration of use • when to seek help while using the method.[D/GPP]		
All health professionals advising women about contraceptive choices should be competent to: • assist women to consider and compare the risks and benefits of all methods relevant to their individual needs • manage common side-effects [D/GPP]		
All health professionals providing contraceptive care should ensure that they have an agreed mechanism in place for referring women for LARC if they do not provide LARC within their own practice/service. [D/GPP]		

All health professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. [D/GPP]	Guidance for training for doctors and nurses can be obtained from the FFPRHC (Faculty of Family Planning and Reproductive Health Care) and the RCN (Royal College of Nursing) respectively

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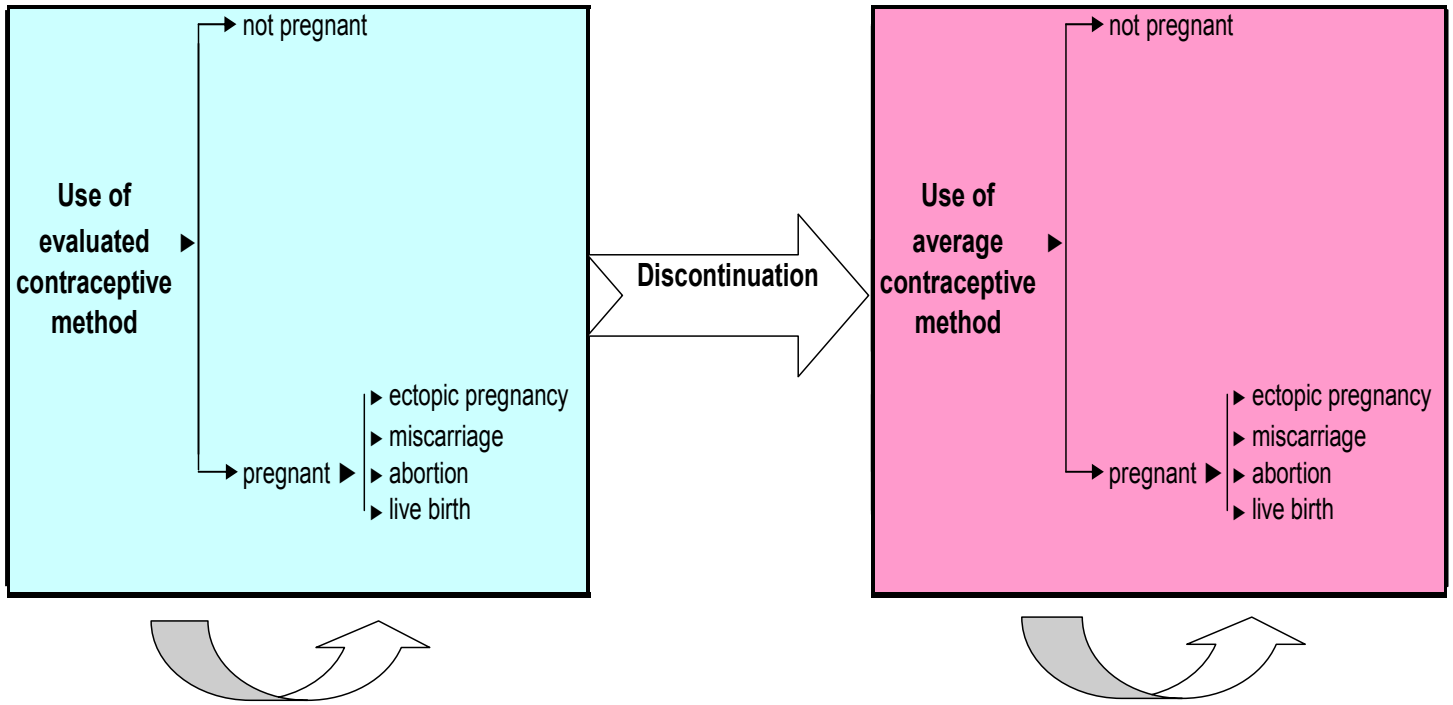
Appendix A

Information for the public (This will be available in the second draft of this guideline)

Appendix B

Schematic structure of the decision-analytic model used in the economic analysis



The diagram shows the two states of the decision model: the state of using one of the contraceptive methods evaluated in the economic analysis, and the following state of using the average contraceptive method; while being on any of these states, a woman under contraceptive protection may not become pregnant, or she may experience an unintended pregnancy due to contraceptive failure (with all the associated

outcomes). All women in the hypothetical cohort enter the state of using one of the contraceptive methods evaluated; from this state, a woman may discontinue and move to the state of the average contraceptive method, or she may remain on the method evaluated; once moving to the state of the average contraceptive method, the woman remains on it for the rest of the time-frame examined.

Appendix C Results of sensitivity analysis

1. Changes in failure rates of IUD by ± 10%

The table shows the ranges of ICERs between the IUD and the other LARC methods resulting from changing the base-case value of the IUD failure rate by ± 10%.

Ranges of ICERs between IUD and the other LARC methods			
Time frame	**Implant vs IUD (+10% / - 10%)**	**IUS vs IUD (+10% / - 10%)**	**IUD vs Injectable (+10% / - 10%)**
1 year of use	£18,715 - £25,259	£44,117 - £94,542	£389 - £292
2 years of use	£25,928 - £49,853	IUD dominates	IUD dominates
3 years of use	£28,413 - £80,128	IUD dominates	IUD dominates
4 years of use	£25,728 - £36,947	IUD dominates	IUD dominates
5 years of use	£9,536 - £11,208	£14,683 - £25,918	IUD dominates
6 years of use	£4,822 - £5,381	£12,661 - £16,185	IUD dominates
7 years of use	£5,062 - £5,495	£7,766 - £9,266	IUD dominates
8 years of use	£3,621 - £3,899	£5,463 - £6,332	IUD dominates
9 years of use	£2,135 - £2,300	£2,879 - £3,325	IUD dominates
10 years of use	£2,623 - £2,795	£2,189 - £2,519	IUD dominates
11 years of use	£2,124 - £2,262	£3,300 - £3,695	IUD dominates
12 years of use	£1,747 - £1,862	£2,772 - £3,096	IUD dominates
13 years of use	£2,091 - £2,213	£2,366 - £2,640	IUD dominates
14 years of use	£1,805 - £1,912	£2,044 - £2,281	IUD dominates
15 years of use	£1,570 - £1,665	£1,783 - £1,992	IUD dominates

2. Changes in discontinuation rates of LARC by ± 10%

Comparisons between LARC methods and male / female sterilisation

The tables below show the ranges of ICERs and cases of dominance between LARC methods and male/female sterilisation resulting from changing the base-case values of discontinuation rates of LARC methods by ± 10%. Results are shown for up to 5 years of contraceptive use regarding male sterilisation and up to 8 years of use regarding female sterilisation, as from this time period and above both methods of sterilisation become dominant options over any LARC method under this scenario, and no further changes in the results occur.

Ranges of ICERs / cases of dominance between male sterilisation & LARC methods				
Time frame	**MS vs IUD (+ 10% / - 10%)**	**MS vs Implant (+ 10% / - 10%)**	**MS vs IUS (+ 10% / - 10%)**	**MS vs injectable (+ 10% / - 10%)**
1 year of use	£14,294 - £17,143	£12,591 -£16,277	£10,678 - £13,659	£7,618 - £9,665
2 years of use	£3,338 - £4,363	£2,181 - £3,112	£1,830 - £2,648	£1,037 - £1,477
3 years of use	£936 - £1,486	£320 - £787	£190 - £615	MS dominates
4 years of use	£11 - £365	MS dominates	MS dominates	MS dominates
5 years of use	MS dominates	MS dominates	MS dominates	MS dominates

MS: male sterilisation

Ranges of ICERs / cases of dominance between female sterilisation & LARC methods				
Time frame	**FS vs IUD (+ 10% / - 10%)**	**FS vs Implant (+ 10% / - 10%)**	**FS vs IUS (+ 10% / - 10%)**	**FS vs injectable (+ 10% / - 10%)**
1 year of use	£35,799 - £44,260	£39,107 - £53,566	£32,789 - £43,566	£17,024 - £21,792
2 years of use	£8,574 - £10,832	£7,473 - £9,850	£6,684 - £8,760	£3,679 - £4,745
3 years of use	£3,473 - £4,603	£2,847 - £3,951	£2,592 - £3,600	£1,316 - £1,809
4 years of use	£1,573 - £2,281	£751 - £1,203	£1,106 - £1,745	£353 - £615
5 years of use	£659 - £1,161	£138 - £465	£379 - £839	FS dominates
6 years of use	£161 - £549	FS dominates - £51	FS dominates	FS dominates
7 years of use	FS dominates - £173	FS dominates	FS dominates	FS dominates
8 years of use	FS dominates	FS dominates	FS dominates	FS dominates

FS: female sterilisation

Comparisons across LARC methods: IUS, IUD, and implant

a. Comparisons between IUD - IUS

Years of use	Varying IUS discontinuation rates		Varying IUD discontinuation rates	
	+10%	-10%	+10%	-10%
1	IUD dominates	IUS vs IUD £25,117	IUS vs IUD £28,041	IUD dominates
2	IUD dominates	IUS vs IUD £20,745	IUS vs IUD £27,205	IUD dominates
3	IUD dominates	IUS vs IUD £8,855	IUS vs IUD £10,610	IUD dominates
4	IUD dominates	IUS vs IUD £3,272	IUS vs IUD £3,581	IUD dominates
5	IUD dominates	IUS vs IUD £1,240	IUS vs IUD £1,297	IUD dominates
6	IUD dominates	IUS vs IUD £2,506	IUS vs IUD £2,271	IUD dominates
7	IUD dominates	IUS vs IUD £1,585	IUS vs IUD £1,377	IUD dominates
8	IUD dominates	IUS vs IUD £1,026	IUS vs IUD £843	IUD dominates
9	IUD dominates	IUS vs IUD £190	IUS vs IUD £110	IUD dominates
10	IUD dominates	IUS dominates	IUS dominates	IUD dominates
11	IUD dominates	IUS vs IUD £525	IUS vs IUD £361	IUD dominates
12	IUD dominates	IUS vs IUD £336	IUS vs IUD £185	IUD dominates
13	IUD dominates	IUS vs IUD £184	IUS vs IUD £45	IUD dominates
14	IUD dominates	IUS vs IUD £61	IUS dominates	IUD dominates
15	IUD dominates	IUS dominates	IUS dominates	IUD dominates

b. Comparisons between implant - IUS

Years of use	Varying implant discontinuation rates		Varying IUS discontinuation rates	
	+10%	-10%	+10%	-10%
1	Implant dominates	Implant dominates	Implant dominates	Implant dominates
2	IUS vs implant £1,347	Implant dominates	Implant dominates	IUS vs implant £778
3	IUS dominates	Implant dominates	Implant dominates	IUS dominates
4	IUS dominates	Implant vs IUS £2,557	Implant vs IUS £2,144	IUS dominates
5	IUS dominates	Implant vs IUS £1,298	Implant vs IUS £992	IUS dominates
6	IUS dominates	Implant dominates	Implant dominates	IUS dominates
7	IUS dominates	Implant vs IUS £365	Implant vs IUS £186	IUS dominates
8	IUS dominates	Implant vs IUS £58	Implant dominates	IUS dominates
9	IUS dominates	Implant dominates	Implant dominates	IUS dominates
10	IUS dominates	Implant vs IUS £567	Implant vs IUS £336	IUS dominates
11	IUS dominates	Implant dominates	Implant dominates	IUS dominates
12	IUS dominates	Implant dominates	Implant dominates	IUS dominates
13	IUS dominates	Implant vs IUS £119	Implant dominates	IUS dominates
14	IUS dominates	Implant dominates	Implant dominates	IUS dominates
15	IUS dominates	Implant dominates	Implant dominates	IUS dominates

c. Comparisons between implant - IUD

Years of use	Varying implant discontinuation rates		Varying IUD discontinuation rates	
	+10%	-10%	+10%	-10%
1	Implant vs IUD £43,111	Implant vs IUD £13,865	Implant vs IUD £14,489	Implant vs IUD £38,746
2	IUD dominates	Implant vs IUD £8,134	Implant vs IUD £8,898	IUD dominates
3	IUD dominates	Implant vs IUD £4,216	Implant vs IUD £4,624	IUD dominates
4	IUD dominates	Implant vs IUD £6,347	Implant vs IUD £6,199	IUD dominates
5	IUD dominates	Implant vs IUD £3,124	Implant vs IUD £2,890	IUD dominates
6	IUD dominates	Implant vs IUD £1,654	Implant vs IUD £1,445	IUD dominates
7	Implant vs IUD £230,903	Implant vs IUD £2,126	Implant vs IUD £1,800	IUD dominates
8	Implant vs IUD £39,002	Implant vs IUD £1,455	Implant vs IUD £1,176	Implant vs IUD £78,536
9	Implant vs IUD £17,805	Implant vs IUD £672	Implant vs IUD £493	Implant vs IUD £29,334
10	Implant vs IUD £16,301	Implant vs IUD £1,040	Implant vs IUD £795	Implant vs IUD £25,571
11	Implant vs IUD £12,406	Implant vs IUD £761	Implant vs IUD £540	Implant vs IUD £18,996
12	Implant vs IUD £10,015	Implant vs IUD £545	Implant vs IUD £344	Implant vs IUD £15,165
13	Implant vs IUD £10,449	Implant vs IUD £795	Implant vs IUD £552	Implant vs IUD £15,744
14	Implant vs IUD £9,048	Implant vs IUD £624	Implant vs IUD £398	Implant vs IUD £13,601
15	Implant vs IUD £7,992	Implant vs IUD £481	Implant vs IUD £270	Implant vs IUD £12,014

3. Perfect use of male condom / COC

Perfect use of male condom - results for up to 4 years of contraceptive use

1 year of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	15	263,613	Implant vs condom: £43,128/pregnancy averted
Implant/condom	15	289,103	Implant/condom vs condom: £48,360/pregnancy averted
IUS	17	270,749	IUS vs condom: £73,558/pregnancy averted
IUS/condom	17	295,998	IUS/condom vs condom: £82,106/pregnancy averted
IUD	18	195,442	IUD vs male condom: £83,248/pregnancy averted
IUD/condom	18	221,176	IUD/condom vs condom: £98,339/pregnancy averted
CONDOM	20	53,488	
Injectable	33	190,534	Dominated by condom
Injectable/condom	33	212,075	Dominated by condom alone

2 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
CONDOM	39	105,167	
Implant	53	325,806	Dominated by condom
Implant/condom	53	370,694	Dominated by condom alone
IUD	55	256,572	Dominated by condom
IUD/condom	55	302,326	Dominated by condom alone
IUS	57	337,093	Dominated by condom
IUS/condom	57	381,382	Dominated by condom alone
Injectable	99	338,376	Dominated by condom
Injectable/condom	99	373,190	Dominated by condom alone

3 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
CONDOM	58	155,098	
Implant	104	405,577	Dominated by condom
Implant/condom	104	466,036	Dominated by condom alone
IUD	105	337,207	Dominated by condom
IUD/condom	105	398,902	Dominated by condom alone
IUS	109	418,616	Dominated by condom

IUS/condom	109	478,387	Dominated by condom alone
Injectable	167	482,178	Dominated by condom
Injectable/condom	167	528,857	Dominated by condom alone

1

4 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
CONDOM	76	203,341	
Implant	161	584,349	Dominated by condom
Implant/condom	161	658,052	Dominated by condom alone
IUD	166	432,018	Dominated by condom
IUD/condom	166	506,401	Dominated by condom alone
IUS	167	508,869	Dominated by condom
IUS/condom	167	581,728	Dominated by condom alone
Injectable	234	622,935	Dominated by condom
Injectable/condom	234	680,503	Dominated by condom alone

2

3

4 **Perfect use of COC – results for up to 15 years of contraceptive use**

5

1 year of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	15	263,613	Implant vs COC: £6,548/pregnancy averted
IUS	17	270,749	IUS vs COC: £7,945/pregnancy averted
IUD	18	195,442	IUD vs COC: £2,858/pregnancy averted
COC	31	158,711	
Injectable	33	190,534	Dominated by COC

6

7

2 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	53	325,806	Implant vs COC: £1,093/pregnancy averted
IUD	55	256,572	IUD dominates COC
IUS	57	337,093	IUS vs COC: £1,551/pregnancy averted
COC	92	283,429	
Injectable	99	338,376	Dominated by COC

8

9

3 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	104	405,577	Implant dominates COC
IUD	105	337,207	IUD dominates COC
IUS	109	418,616	IUS vs COC: £180/pregnancy averted

COC	156	410,021	
Injectable	167	482,178	Dominated by COC

1

4 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	161	584,349	Implant vs COC: £735/pregnancy averted
IUD	166	432,018	IUD dominates COC
IUS	167	508,869	IUS dominates COC
COC	224	537,630	
Injectable	234	622,935	Dominated by COC

2

3

5 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	219	672,035	Implant vs COC: £86/pregnancy averted
IUS	228	603,534	IUS dominates COC
IUD	232	534,555	IUD dominates COC
COC	294	665,531	
Injectable	302	760,600	Dominated by COC

4

5

6 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	276	757,841	Implant dominates COC
IUS	290	767,736	IUS dominates COC
IUD	299	636,652	IUD dominates COC
COC	366	793,112	
Injectable	370	895,141	Dominated by COC

6

7

7 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	331	914,756	Implant dominates COC
IUS	351	859,181	IUS dominates COC
IUD	365	736,023	IUD dominates COC
Injectable	437	1,026,537	Injectable vs COC: £58,242/pregnancy averted
COC	439	919,863	

8

9

8 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	385	996,365	Implant dominates COC
IUS	409	948,186	IUS dominates COC
IUD	429	832,635	IUD dominates COC

Injectable	504	1,154,780	Injectable vs COC: £12,959/pregnancy averted
COC	512	1,045,355	

1

9 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	438	1,075,916	Implant dominates COC
IUS	466	1,034,800	IUS dominates COC
IUD	491	958,830	IUD dominates COC
Injectable	570	1,279,871	Injectable vs COC: £6,988/pregnancy averted
COC	586	1,169,238	

2

3

10 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	490	1,217,464	Implant dominates COC
IUS	522	1,119,079	IUS dominates COC
IUD	551	1,050,425	IUD dominates COC
Injectable	635	1,401,818	Injectable vs COC: £4,655/pregnancy averted
COC	659	1,291,222	

4

5

11 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	540	1,293,020	Implant dominates COC
IUS	576	1,256,971	IUS dominates COC
IUD	610	1,139,234	IUD dominates COC
Injectable	700	1,520,639	Injectable vs COC: £3,420/pregnancy averted
COC	732	1,411,073	

6

7

12 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	588	1,366,633	Implant dominates COC
IUS	629	1,336,833	IUS dominates COC
IUD	667	1,225,501	IUD dominates COC
Injectable	764	1,636,357	Injectable vs COC: £2,661/pregnancy averted
COC	804	1,528,602	

8

9

13 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	636	1,494,323	Implant dominates COC
IUS	680	1,414,530	IUS dominates COC
IUD	722	1,309,296	IUD dominates COC

Injectable	826	1,749,003	Injectable vs COC: £2,149/pregnancy averted
COC	875	1,643,663	

1

14 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	682	1,564,174	Implant dominates COC
IUS	730	1,490,079	IUS dominates COC
IUD	776	1,390,690	IUD dominates COC
Injectable	888	1,858,611	Injectable vs COC: £1,782/pregnancy averted
COC	945	1,756,143	

2

3

15 years of use	Total pregnancies	Total costs (£)	Incremental Cost-effectiveness Ratios
Implant	727	1,632,199	Implant dominates COC
IUS	778	1,563,548	IUS dominates COC
IUD	828	1,469,754	IUD dominates COC
Injectable	948	1,965,220	Injectable vs COC: £1,507/pregnancy averted
COC	1014	1,865,957	

4

5

Long Acting Reversible Contraception: Evidence tables

Chapter 3 Contraceptive use and principles of Care

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1] Tanfer 2000 [81] USA	[2] Survey	[3] 3	[4] 1075	[5] women aged 20-37	[6] NA	[7] NA	[8]	[9] Usage of LARC Reasons for not using LARC: A) Lack of knowledge B) satisfied with current method C) Fears methods D) Methods costs too much E) Had no interst/does not know	[10] Implants: <2% Injectables: <3% A) Implants: 9.3% Injectables: 27.1% B) Implants: 28.1% Injectables: 20.6% C) Implants: 22% Injectables: 17% D) Implants: 2.3% Injectables: 1.9% E) Implants: 12.2% Injectables: 6.9%	[11] US National Survey of Women	[12]

1

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Backman 2002 [67] Finland	Survey	3	23,885	Women with IUS	NA	NA		User satisfaction as a result of advance information on A) Amenorrhoea B) Bleeding problems C) PID D) Greasy hair/skin E) mood changes F) possibility of pregnancy	'A lot of ' vs 'very little' information A) OR 4.96 (95% CI 4.15 to 5.93) B) OR 3.28 (95% CI 2.61 to 4.10) C) OR 2.52 28 (95% CI 2.24 to 2.82) D) OR 2.35 28 (95% CI 2.09 to 2.65) E) OR 2.32 28 (95% CI 2.06 to 2.61) F) OR 2.27 28 (95% CI 1.99 to 2.59)		Response rate 75%

1

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Van Lunsen 1994 [59] The Netherlands	Questionnaire survey	3	4560	Women aged 15-49	NA	NA		Choices in contraceptive use Sources of information on contraceptive use A) GP B) Parents C) Friends D) Magazines E) School and health education materials F) TV G) Family Planning Clinic	Women's own decision: 89% A) 73% B) 32% C) 3% D): 21% E): 14% F) 11% G) 5%		Response rate: 39%
Davie 1996 [453] UK	Questionnaire survey	3	Physicians at 6 family planning centres on experience in 521 patients	Women aged 17 -47, with implant inserted	NA	NA		Frequency of counselling before implant insertion Person responsible for counselling; A) Physician B) Nurse Physician's perception of patient acceptance: A) well and moderately received B) Fairly and poorly received	100% A) 78% B) 39% A) 80% B) 20%		

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Canto de Cetina 2001[69] Mexico	RCT	1-	350 women	Women aged 18-35 of proven fertility, not breastfeeding	Structured counselling on bleeding problems and other side effects (n=175)	Routine counselling (n=175)	1 year	Discontinuation rate	Due to menstrual disturbances (amenorrhoea, irregular and heavy bleeding) 8.6% vs 32% Due to othe medical events (weight gain, vomiting, dizziness, depression and loss of libido) 6.3% vs 7.4% Total discontinuation: 17% vs 43%	Not stated	

1

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Lei 1996 [283] China	Non-RCT	2+	204	DMPA users aged 18 to 40, including breastfeeding mothers	Structured pre-treatment and ongoing counsellingon side-effects of DMPA (n=204)	Routine counselling (n=217)	1 year	Discontinuation rate	Due to all medical events (irregular bleeding, amenorrhoea and other events): 5.9% vs 26% Due to: Missing injection 0.5% vs 4% Personal reasons: 4% vs 8.5% Lost to follow-up 0% vs 8.5% Protocol violation: 1% vs 0% Total discontinuation: 11.3% vs 42%	Bational Research Institute for Family Planning, Beijing Upjohn	

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Steiner 2003 [71] USA	RCT	1+	461	Women aged 18-44 years	FDA table (Numbers table) (n=147)	WHO table (Numbers and categories table) (n=144) Category table (n=142)		Table provides enough information to choose contraception Communication of contraceptive effectiveness 'Table difficult to read'	FDA vs WHO vs categories 85% vs 855 vs 77% Significant improvement: FDA vs WHO vs categories 20% vs 19% vs 37% FDA vs WHO vs categories 19% vs 15% vs 6%	Not stated	Clear method of randomisation and concealment

Chapter 5 Copper Intra-uterine devices

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Arowojolu 1995[126] **Nigeria**	**RCT**	**1-**	**300**	**Sexually active women requesting contraception**	**TCu380A (n=100)**	**MLCu250 (n=100)** **MLCu375 (n=100)**	**1 year**	**Cumulative probability (%) for discontinuation at 1 year due to:** **A) Pregnancy B) Expulsion** **C) PID** **Complications during insertions (%):** **A) Failure** **B) Cervical trauma** **C) Syncope** **D) Pelvic pain** **Events after insertion (%):** **A) PID** **B) Hospitalisation due to PID** **C) Menorrhagia** **D) Amenorrhoea** **E) Intermenstrual bleeding** **F) Dysmenorrhoea** **G) Perforation** **H) Total expulsion**	**At 1 year:** **A) T380A: 1.1** **ML375: 0** **ML250: 0** **B) T380A: 4.1** **ML375: 0** **ML250: 3.1** **C) T380A: 1.2** **ML375: 1.0** **ML250: 5.2** **During insertion:** **A) T380A: 1** **ML375: 0** **ML250: 0** **B) T380A: 0** **ML375: 0** **ML250: 0** **C) T380A: 0** **ML375: 0** **ML250: 0** **D) T380A: 6** **ML375: 1** **ML250: 2** **After insertion:** **A) T380A: 2** **ML375: 2** **ML250: 7** **B) T380A: 1** **ML375: 0** **ML250: 1** **C) T380A: 4** **ML375: 5** **ML250: 2** **D) T380A: 2** **ML375: 2** **ML250: 1** **E) T380A: 6** **ML375: 4** **ML250: 4**	**Not stated**	**Women randomly selected an envelope which specified device allocation** **Insertions performed during the menstrual cycle**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									F) T380A: 27 **ML375: 24** **ML250: 21** **G) T380A: 1** **ML375: 0** **ML250: 0** **H) T380A: 2** **ML375: 0** **ML250: 2**		
Cole 1985[128] **5 centres in Yugoslavia, Panama, Costa Rica, and Egypt**	**Multicentre RCT**	**1-**	**1477**	**Women requesting IUD insertion**	**TCu380Ag (n=737)**	**MLCu375 (n=740)**	**1 year**	**Cumulative discontinuation rates per 100 women (SE), standardised for age, at 1 year due to:** **A) Pregnancy** **B) Expulsion** **C) Perforation** **D) Removal for bleeding or pain** **Continuation rate** **Complications/ complaints during insertions (%):** **A) Failed insertion** **B) Dilatation** **C) Cervical laceration** **D) Syncope** **E) Pelvic pain** **Events after insertion (%):** **A) PID** **B) Hospitalisation**	**At 1 year (582 and 574 women remaining for T380Ag and ML375 respectively):** **A) T380Ag: 0.3 (0.2)** **ML375: 0.8 (0.4)** **B) T380Ag: 3.3 (0.7)** **ML375: 4.1 (0.8)** **C) T380Ag: 0 (0.0)** **ML375: 0 (0.0)** **D) T380Ag: 3.6 (0.7)** **ML375: 3.6 (0.8)** **Continuation rate:** **For T380Ag: 90.9 (1.1)** **For ML375: 88.7 (1.2)** **During insertion:** **A) T380Ag: 0.1** **ML375: 0.1** **B) T380Ag: 4.1** **ML375: 3.9** **C) T380Ag: 1.7** **ML375: 1.6** **D) T380Ag: 0.3** **ML375: 0** **E) T380Ag: 7.9** **ML375: 7.3** **After insertion:** **A) T380Ag: 3.8** **ML375: 2.8** **B) T380Ag: 0.3** **ML375: 0.3**	**Family Health International and the US Agency for International Development**	**Method of random allocation not specified; proportion of T380Ag users aged under 25 years was significantly higher (34.5% vs 31.0%, p<0.05)** **All insertions performed during menstruation**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								due to heavy menstrual bleeding **C) Dysmenorrhoea** **D) Intermenstrual bleeding** **E) Intermenstrual spotting** **F) Intermenstrual pelvic pain**	**C) T380Ag: 48.6** **ML375: 44.5** **D) T380Ag: 8.3** **ML375: 9.7** **E) T380Ag: 17.2** **ML375: 16.4** **F) T380Ag: 24.2** **ML375: 18.5*** **** difference between the two devices significant at p<0.05***		
Champion 1988[127] **3 centres in Yugoslavia and Panama**	**Multicentre RCT**	**1+**	**885**	**Women, aged 18 to 40 years, requesting intrauterine contraception** **Exclusions: pregnancy, uterine abnormalities, evidence of pelvic infection, anaemia, history of ectopic pregnancy, severe PID, menorrhagia, hypermenorrhoea**	**TCu380Ag (n=441)**	**MLCu375 (n=444)**	**3 years**	**Cumulative discontinuation rates per 100 women, standardised for age and parity, at 2 and 3 years due to:** **A) Pregnancy** **B) Expulsion** **C) Removal for bleeding or pain** **Discontinuation rate** **Loss to follow-up** **Complications/ complaints during insertions (%):** **A) Failed insertion** **B) Dilatation** **C) Cervical laceration**	**At 2 years:** **A) T380Ag: 0.6** **ML375: 1.3** **B) T380Ag: 4.5** **ML375: 5.6** **C) T380Ag: 7.8** **ML375: 7.6** **Continuation rate:** **For T380Ag: 20.3** **For ML375: 23.4** **At 3 years:** **A) T380Ag: 0.6** **ML375: 1.8** **B) T380Ag: 5.4** **ML375: 6.5** **C) T380Ag: 8.8** **ML375: 11.4** **Discontinuation rate:** **For T380Ag: 32.6** **For ML375: 38.6** **Loss to follow-up at the end of 3 years:** **For T380Ag: 102 women** **For ML375: 106 women**	**Family Health International and the US Agency for International Development**	**A continuation of the Cole study[128]** **Random allocation by opaque envelopes prepared by Family Health International; mean age and mean parity were higher in the ML375 group (27.5 vs. 26.4 years, p<0.05; 1.7 vs. 1.5 births, p<0.05)**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								D) Pain **Events after insertion (%):** **A) PID** **B) Hospitalisation due to bleeding**	**During insertion:** **A) T380Ag: 0** **ML375: 0.2** **B) T380Ag: 6.6** **ML375: 5.4** **C) T380Ag: 0.9** **ML375: 0.9** **D) T380Ag: 6.0** **ML375: 4.0** **After insertion:** **A) T380Ag: 7.0** **ML375: 4.6** **B) T380Ag: 0.5** **ML375: 0.5**		
Sastrawinata 1991[129] **6 centres in Indonesia**	**Multicentre RCT**	**1+**	**1894**	**Sexually active women, aged of 18 to 40 years, with no contraindications to IUDs** **Exclusions: no IUD use in the month prior to enrolment in study, <41 days since last pregnancy**	**TCu380A (n=946)**	**MLCu375 (n=948)**	**2 years**	**Cumulative discontinuation rates per 100 women (SE) at 1 and 2 years due to:** **A) Pregnancy** **B) Expulsion or displacement** **C) Medical removal for bleeding or pain**	**At 1 year:** **A) T380A: 0.4 (0.2)** **ML375: 1.4 (0.4)*** **B) T380A: 6.0 (0.8)** **ML375: 3.8 (0.6)** **C) T380A: 1.6 (0.4)** **ML375: 1.1 (0.4)** **At 2 years:** **A) T380A: 1.2 (0.4)** **ML375: 2.7 (0.6)** **B) T380A: 6.7 (0.8)** **ML375: 5.3 (0.8)** **C) T380A: 2.3 (0.5)** **ML375: 1.7 (0.4)** **** difference between the two devices significant at p=0.04***	**US Agency for International Development**	**Study contained data on a third device which was not included as it is not currently licensed in the UK** **Computer generated random allocation by sealed envelopes**
UNDP 1994[130] **19 centres in nine developing countries**	**Multicentre RCT**	**1++**	**3655**	**Women volunteers** **Exclusions: nulliparous, history of PID or pelvic abscess since last pregnancy, <6 weeks**	**TCu380A (n=1823)**	**MLCu375 (n=1832)**	**3 years**	**Cumulative discontinuation rates per 100 women (SE) at 1, 2 and 3 years due to:** **A) Intrauterine**	**At 1 year (1607 and 1632 women remaining for T380A and ML375 respectively):** **A) T380A: 0.8 (0.2)** **ML375: 1.2 (0.3)** **B) T380A: 0** **ML375: 0**	**Not stated**	**Computer generated random allocation by sealed envelopes in blocks of ten**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				since parturition or abortion, history of ectopic pregnancy, recent STI, undiagnosed genital tract bleeding, known/suspected genital tract malignancy, multiple fibromyomas associated with menstrual disorders, evidence of anaemia, and history of hytidaform mole in last pregnancy				**pregnancy B) Ectopic C) Expulsion Continuation rate**	**C) T380A: 3.8 (0.5) ML375: 3.6 (0.4) Continuation rate: For T380A: 88.2 (0.8) For ML375: 89.1 (0.7) At 2 years (1468 and 1481 women remaining for T380A and ML375 respectively): A) T380A: 1.2 (0.3) ML375: 2.2 (0.4)* B) T380A: 0.2 (0.1) ML375: 0 C) T380A: 4.7 (0.5) ML375: 5.2 (0.5) Continuation rate: For T380A: 82.0 (0.9) For ML375: 82.2 (0.9) At 3 years (1014 women remaining for each device) A) T380A: 1.4 (0.3) ML375: 2.8 (0.4)* B) T380A: 0.2 (0.1) ML375: 0.1 (0.1) C) T380A: 5.2 (0.5) ML375: 6.4 (0.6) Continuation rate: For T380A: 77.9 (1.0) For ML375: 77.7 (1.0) ** difference between the two devices significant at p<0.05***		
Reinprayoon 1998[454] 11 centres in Thailand	**Multicentre RCT**	**1+**	**1396**	**Sexually active women, aged 18 to 40 years, with no contraindications to IUD use**	**TCu380A (n=681)**	**MLCu250 (n=715)**	**1 year**	**Cumulative discontinuation rates per 100 women (SE) at 1 year due to: A) Pregnancy B) Expulsion or**	**At 1 year: A) T380A: 0.2 (0.2) ML250: 1.0 (0.4) B) T380A: 2.4 (0.6) ML250: 4.6 (0.8) C) T380A: 0.9 (0.4) ML250: 0.7 (0.3)**	**Family Health International and the US Agency**	**Random allocation by sealed envelopes IUD inserted during the interval**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								displacement **C) Medical removal for bleeding or pain** **Discontinuation rate** **Loss to follow-up (%)** **Complications/ complaints during insertions (%):** **A) Cervical laceration** **B) Pelvic pain** **C) Syncope** **Events after insertion (%):** **A) Hospitalisation** **B) Dysmenorrhea** **C) Intermenstrual pelvic pain** **D) Intermenstrual bleeding** **E) PID**	**Discontinuation rate:** **For T380A: 9.8 (1.2)** **For ML259: 12.5 (1.3)** **Loss:** **For T380A: 15.4** **For ML259: 13** **During insertion:** **A) T380A: 0.6** **ML259: 1.0** **B) T380A: 10.7** **ML259: 8.4** **C) T380A: 0** **ML259: 0.1** **After insertion:** **A) T380A: 0.8** **ML259: 0.3** **B) T380A: 59.1** **ML259: 44.4*** **C) T380A: 47.9** **ML259: 38.5*** **D) T380A: 35.4** **ML259: 29.3**** **E) T380A: 2.8** **ML259: 1.9** **** difference between the two devices significant at p<0.01*** ***** difference between the two devices significant at p=0.02***	**for International Development**	**period**
Farr 1994[455] **4 sites in 3 countries (Sri Lanka (2), Thailand (1), Malaysia (1)**	**Multicentre RCT**	**1+**	**2043**	**Sexually active women aged 18 to 40 years**	**TCu380A (n=1008)**	**MLCu250 (n=1035)**	**1 year**	**Cumulative discontinuation rates per 100 women (SE) at 1 year due to:** **A) Pregnancy** **B) Expulsion** **C) Medical**	**At 1 year (805 and 822 women remaining for T380A and ML250 respectively):** **A) T380A: 0.2 (0.15)** **ML250: 1.2 (0.36)*** **B) T380A: 2.7(0.52)** **ML250: 3.7 (0.62)** **C) T380A: 3.0 (0.57)**	**Family Health International and the US Agency for**	**Random allocation by sealed envelopes prepared by Family Health International**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								removal for bleeding or pain **Discontinuation rate** **Loss to follow-up (%)** **Complications during insertions (%):** **A) Dilatation** **B) Cervical laceration** **C) Pelvic pain** **Events after insertion (%):** **A) Dysmenorrhoea** **B) Intermenstrual bleeding** **C) Intermenstrual pelvic pain**	**ML250: 2.8 (0.54)** **Discontinuation rate:** **For T380A: 9.9 (0.98)** **For ML250: 11.4 (1.02)** **Loss:** **For T380A: 11** **For ML250: 10** **During insertion:** **A) For T380A: 0.4** **For ML250: 0.0** **B) For T380A: 0.4** **For ML250: 0.6** **C) For T380A: 13.6** **For ML250: 12.8** **After insertion:** **A) For T380A: 49** **For ML250: 35.6**** **B) For T380A: 27.4** **For ML250: 24.4** **C) For T380A: 34.7** **For ML250: 28.7**** **** difference between the two devices significant at p=0.01*** ***** difference between the two devices significant at p<0.01***	**International Development**	
Rosenberg 1996 [137] **22 sites across Europe and the USA**	**Multicentre RCT**	**1+**	**427**	**Women aged 18 to 40 years who were at least 3 months post-partum or post second trimester abortion, or 1 month post first trimester abortion and had at least 1 normal or withdrawal bleeding episode**	**TCu380A (n=427)**	**CU-Fix* (n=447)** **** Data not shown for this device***	**2 years**	**Cumulative discontinuation rates per 100 women (SE) at 1 and 2 years due to:** **A) Pregnancy** **B) Expulsion** **C) Medical removal for bleeding or pain** **D) Medical**	**At 1 year (230 women remaining):** **A) 0.0 (0.0)** **B) 2.0 (0.7)** **C) 6.9 (1.4)** **D) 1.0 (0.6)** **Continuation rate: 86.2 (2.1)** **At 2 years (61 women remaining):** **A) 0.0 (0.0)**	**GynoPharma (manufacturer of both devices used in this study)**	**Computer generated random allocation in blocks of four**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: Nulliparous, history of ectopic pregnancy, PID, or infection with gonorrhoea or Chlamydia, diabetes, jaundice or anaemia				**removal for PID** **Continuation rate**	**B) 2.0 (0.7)** **C) 11.4 (2.3)** **D) 1.0 (0.6)** **Continuation rate: 78.3 (4.7)**		
UNDP 1995[138] **22 centres in 13 developing countries**	**Multicentre RCT**	**1++**	**2184**	**Women volunteers** **Exclusions: nulliparous, history of PID or pelvic abscess since last pregnancy, <6 weeks since parturition or abortion, history of ectopic pregnancy, recent STI, undiagnosed genital tract bleeding, known/suspected genital tract malignancy, multiple fibromyomas associated with menstrual disorders, evidence of anaemia, or history of hytidaform mole in last pregnancy**	**TCu380A (n=2184)**	**Frameless FlexiGard* (n=2102)** ***Data not shown for this device***	**3 years**	**Cumulative discontinuation rates per 100 women (SE) at 1, 2 and 3 years due to:** **A) Intrauterine pregnancy** **B) Ectopic** **C) Expulsion** **D) Medical removal** **E) Medical removal for bleeding or pain** **F) Medical removal for PID** **Continuation rate**	**At 1 year (1774 women remaining):** **A) 0.5 (0.2)** **B) 0.1 (0.1)** **C) 2.4 (0.3)** **D) 4.0 (0.4)** **E) 3.6 (0.4)** **F) 0.3 (0.1)** **Continuation rate: 89.9 (0.7)** **At 2 years (1435 women remaining):** **A) 1.0 (0.2)** **B) 0.1 (0.1)** **C) 3.4 (0.4)** **D) 6.7 (0.6)** **E) 6.1 (0.6)** **F) 0.4 (0.2)** **Continuation rate: 82.9 (0.9)** **At 3 years (1061 women remaining):** **A) 1.6 (0.3)** **B) 0.1 (0.1)** **C) 4.4 (0.5)** **D) 8.3 (0.7)** **E) 7.5 (0.6)** **F) 0.4 (0.2)** **Continuation rate: 77.3 (1.0)**	**Not stated**	**Computer generated random allocation by sealed envelopes in blocks of ten**
Wu 2000[139] **6 centres in**	**Multicentre RCT**	**1+**	**607**	**Women volunteers** **Exclusions:**	**TCu380A (n=305)**	**GyneFix (n=302)**	**3 years**	**Cumulative discontinuation rates* at 1, 2 and**	**At 1 year (281 and 289 women remaining for T380A and GyneFix respectively)**	**Contrel Europe**	**Computer generated random**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
China				**nulliparous, history of PID or pelvic abscess since last pregnancy, <6 weeks since parturition or abortion, history of ectopic pregnancy, recent STI, undiagnosed genital tract bleeding, congenital genital tract malformation, known/suspected genital tract malignancy, multiple fibromyomas associated with menstrual disorders, evidence of anaemia, or history of hytidaform mole in last pregnancy**				**3 years due to:** **A) Pregnancy** **B) Expulsion** **C) Perforation** **D) Medical removal** **E) Medical removal for bleeding or pain** **F) Medical removal for PID** ***no standard errors reported***	**A) T380A: 0.34** **GyneFix: 0** **B) T380A: 4.63** **GyneFix: 2.67** **C) T380A: 0** **GyneFix: 0** **D) T380A: 3.08** **GyneFix: 1.02** **E) T380A: 3.08*** **GyneFix: 0.68** **F) T380A: 0** **GyneFix: 0** **At 2 years (274 and 285 women remaining for T380A and GyneFix respectively)** **A) T380A: 0.34** **GyneFix: 0** **B) T380A: 6.34** **GyneFix: 3.00** **C) T380A: 0** **GyneFix: 0** **D) T380A: 3.43** **GyneFix: 1.71** **E) T380A: 3.43** **GyneFix: 1.38** **F) T380A: 0** **GyneFix: 0** **At 3 years (261 and 274 women remaining for T380A and GyneFix respectively)** **A) T380A: 0.34** **GyneFix: 0** **B) T380A: 7.38**** **GyneFix: 3.00** **C) T380A: 0** **GyneFix: 0** **D) T380A: 6.98** **GyneFix: 5.50** **E) T380A: 6.27** **GyneFix: 4.50** **F) T380A: 0**		**allocation by sealed envelopes in blocks of ten**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									GyneFix: 0 **** difference between the two devices significant at p = 0.32*** ***** difference between the two devices significant at p = 0.018***		
Hui-Qin 1999[456] **China**	**RCT**	**1-**	**100**	**Sexually active women, aged < 40 years old, with normal menstrual bleeding pattern** **Exclusions: nulliparous, clinical evidence or history of ectopic pregnancy or PID, history of diabetes, jaundice or anaemia**	**TCu380A (n=100)**	**FlexiGard* (n=100)** *** Data not shown for this device**	**6 years**	**Cumulative discontinuation rates per 100 women (SE) at 2, 4 and 6 years due to:** **A) Pregnancy B) Partial expulsion C) Complete expulsion D) Medical removal due to bleeding or pain**	**At 2 years:** **A) 1.1 (1.1)** **B) 1.0 (1.1)** **C) 0.0 (0.0)** **D) 1.1 (1.1)** **At 4 years:** **A) 2.2 (1.5)** **B) 3.2 (1.8)** **C) 1.1 (1.1)** **D) 1.1 (1.1)** **At 6 years:** **A) 3.3 (1.9)** **B) 4.3 (2.1)** **C) 1.1 (1.1)** **D) 1.1 (1.1)**	**WHO Special Programme of Research, Development, and Research Training in Human Reproduction**	**Method of random allocation not specified**
O'Brien 2003[457]	**Systematic review**	**1+**	**3 RCTs**	**Women requesting an IUD for contraceptive purposes**							**Two of the RCTs compared devices that are not currently licensed in the UK; please see entries for UNDP 1994[138] and Rosenberg 1996[137] for relevant information extracted from these trials on devices currently licensed in the UK** **Only 1 RCT**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
											compared devices that are currently licensed in the UK; please see entry for Wu 2000[139]
Van Kets 1995[458] **Study site not specified although authors and ethical approval came from Belgium**	**RCT**	**1-**	**600**	**Nulliparous (n=97) and parous (n=503) women, aged 18 to 45 years, requesting intrauterine contraception** **Exclusions:** **< 6 weeks since last pregnancy**	**TCu380A (n=300)**	**Cu-Safe300 (n=300)** **GDG to decide: is CU-Safe300 equiv to Flexi-T300? Currently used in GL text- in table under FlexiT300**	**3 years**	**Cumulative discontinuation rates per 100 women (95% CI) at 1, 2 and 3 years due to:** **A) Pregnancy** **B) Ectopic*** **C) Expulsion** **D) Perforation*** **E) Medical removal for bleeding or pain** **F) Medical removal for PID*** **Discontinuation rate** **** no 95% CI reported***	**At 1 year:** **A) T380A: 0.8 (0.0, 3.0)** **CuSafe: 1.5 (0.4, 3.7)** **B) T380A: 0** **CuSafe: 0.4** **C) T380A: 2.7 (1.1, 5.5)** **CuSafe: 3.6 (1.7, 6.7)** **D) T380A: 0** **CuSafe: 0** **E) T380A: 7.3 (4.1, 10.5)** **CuSafe: 3.8 (1.8, 7.0)** **F) T380A: 0** **CuSafe: 0.4** **Discontinuation rate:** **For T380A: 18.5** **For CUSafe: 14.7** **At 2 years:** **A) T380A: 0.8 (0.0, 3.0)** **CuSafe: 1.9 (0.6, 4.4)** **B) T380A: 0** **CuSafe: 0.4** **C) T380A: 2.7 (1.1, 5.6)** **CuSafe: 6.2 (3.2, 9.2)** **D) T380A: 0** **CuSafe: 0** **E) T380A: 12.9 (8.6, 17.2)** **CuSafe: 7.8 (4.4, 11.2)** **F) T380A: 0** **CuSafe: 0.4** **Discontinuation rate:** **For T380A: 30.4** **For CUSafe: 24.5** **At 3 years:** **A) T380A: 1.5 (0.3, 4.4)**	**Not stated**	**Allocation by 'randomized list'**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									CuSafe: 2.5 (0.9, 5.4) **B) T380A: 0.5** **CuSafe: 0.4** **C) T380A: 2.7 (1.1, 5.5)** **CuSafe: 6.8 (3.6, 10.0)**** **D) T380A: 0** **CuSafe: 0** **E) T380A: 15.6 (10.7, 20.4)†** **CuSafe: 10.4 (6.3, 14.5)** **F) T380A: 0** **CuSafe: 0.4** **Discontinuation rate:** **For T380A: 35.8** **For CUSafe: 31.9** ***** difference between the two devices significant at p<0.0001*** *† difference between the two devices significant at p <0.05*		
WHO 2002 [131] **Multinational: 20 centres**	**RCT**	**1**	**1044**	**Not stated**	**TCu 380A (n= 7334 women years)**	**LNG-IUS (n= 6308 women years)**	**10 years** **Interim results only**	**A) Pregnancy** **B) Ectopic** **C) Expulsion** **D)PID** **E)Discontinuation due to menstrual reasons** **F) Total device-related removals** **G) Loss to follow-up**	**At 6 years:** **A) TCu 380A: 2.0** **LNG-IUS: 0.5** **B) TCu 380A: 0.1** **LNG-IUS: no data** **C) TCu 380A: 8.3** **LNG-IUS: 7.6** **D) TCu 380A: 0.1** **LNG-IUS: 0.3** **E) TCu 380A: 11.0** **LNG-IUS: 35.8** **Amenorrhoea:** **0.5 vs 23.5** **Reduced bleeding:** **3.1 vs 10.9** **Increased bleeding:**		**Ongoing**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								H) No of women completing interval	**7.2 vs 5.4** **F) TCu 380A: 25.6** **LNG-IUS: 47.8** **G) TCu 380A: 7.7** **LNG-IUS: 5.5** **H) TCu 380A: 580** **LNG-IUS: 464**		
Geyoushi 2002[195] **UK**	**Retrospective**	**3**	**138**	**Nulliparous (n=55) and parous (n=83) women using GyneFix at a family planning clinic in Portsmouth from 1997 to 1999**	**Audit through case note review**	**No comparison group**		**A) Accidental pregnancy** **B) Expulsions in first 2 months after insertion** **C) Expulsions from 2 to 12 months** **D) Perforation** **E) Removal for planned pregnancy** **F) Removal for bleeding or pain**	**A) 0** **B) 6 (4.3%)** **C) 5 (3.6%)** **D) 0** **E) 10 (7.2%)** **F) 10 (7.2%)**	**UK Government Department for International Development's Opportunities and Choices knowledge programme**	
Wildemeersch 1994[459] ***Study site not specified although authors and ethical approval came from Belgium, Hungary and Spain***	***Multicentre observational***	***3***	***525***	***Nulliparous (n=199) and parous (n=326) women requesting intrauterine contraception***	***GyneFix***	***No comparison group***	***5 years***	***Cumulative discontinuation rates per 100 women (95% CI) at 5 years due to:*** ***A) Pregnancy*** ***B) Expulsion*** ***C) Perforations*** ***D) Medical removal for bleeding or pain*** ***E) Medical removal for PID***	***At 5 years:*** ***A) 0.9 (0.1, 3.1)*** ***B) 0.3 (0.0, 1.8)*** ***C) 0*** ***D) 3.6 (1.3, 7.7)*** ***E) 0*** ***Discontinuation rate: 32.3*** ***Loss: 11.7 (8.0, 15.4)***	***Not stated***	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Discontinuation rate ***Loss to follow-up***			
Wilson 1989[460] **New Zealand**	**Multicentre RCT**	**1-**	**Not stated (!)**	**Women choosing an intrauterine device as contraception** **Exclusions: pregnancy or suspected pregnancy,history of ectopic pregnancy, repeated expulsions of IUDs, abnormal uterine bleeding, severe dysmenorrhoea, gross congenital abnormality of the uterus, uterus < 6 or > 9cm, uterine fibroids larger than 10 weeks gestation size, endometrial disease, history of PID, gonorrhoea or Chlamydia detected on first visit, dysplasia, acute cervicitis or vaginitis, history of copper or silver allergy or disorder of copper metabolism**	**MLCu375**	**MLAgCu250** **Currently used in GL text in table**	**1 year**	**Cumulative discontinuation rates per 100 women (SE) at 1 year due to:** **A) Pregnancy** **B) Expulsion** **C) Medical removal for bleeding or pain** **D) Medical removal for personal reasons** **Continuation rate** **Loss to follow-up (%)** **Complications during insertions (%):** **A) Failed** **B) 'Difficulty' with insertion** **C) Fainting**	**At 1 year (530 and 540 women remaining for ML375 and MLAg250 respectively):** **A) ML375: 1.3 (1.0)** **MLAg250: 0.2 (0.4)*** **B) ML375: 2.2 (1.3)** **MLAg250: 1.6 (1.1)** **C) ML375: 6.1 (2.2)** **MLAg250: 7.5 (2.3)** **D) ML375: 2.6 (1.5)** **MLAg250: 2.7 (1.5)** **Continuation rate:** **For ML375: 80.9 (3.4)** **For MLAg250: 82.7 (3.5)** **Loss:** **For ML375: 0.6** **For MLAg250: 0.2** **During insertion:** **A) ML375: 0.9** **MLAg250: 0.7** **B) ML375: 3.0** **MLAg250: 2.0** **C) ML375: 1.3** **MLAg250: 0.7** **** difference between the two devices significant at p<0.05***	**Not stated**	**Study contained data on a third device which was not included as it is not currently licensed in the UK** **Random allocation by list of computer generated numbers; however, the number of women originally recruited for each arm was not specified** **All insertion occurred at any time during the menstrual cycle**
Wilson 1992[461] **New Zealand**	**Multicentre RCT**	**1-**	**Not stated (!!)**	**Women choosing an intrauterine device as contraception** **See Wilson[460] (above) for exclusion criteria**	**MLCu375**	**MLAgCu250** **As above, GDG to decide: is MLAgCu250**	**3 years**	**Cumulative discontinuation rates per 100 women (SE) at 2 and 3 years due to:**	**At 2 years (586 and 596 women remaining for ML375 and MLAg250 respectively):** **A) ML375: 2.0 (1.3)** **MLAg250: 3.2 (1.7)** **B) ML375: 2.8 (1.4)**	**Not stated**	**A continuation of previous study by Wilson[460]** **The number of women originally**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
						equiv to MLCu250 (i.e., without silver core) as currently licensed in UK?		**A) Pregnancy B) Expulsion C) Medical removal for bleeding or pain D) Medical removal for personal reasons E) Planning pregnancy Loss to follow-up (%)**	**MLAg250: 2.5 (1.4) C) ML375: 13.5 (3.1) MLAg250: 14.7 (3.1) D) ML375: 10.8 (2.9) MLAg250: 9.2 (2.6) E) ML375: 16.1 (3.3) MLAg250: 13.4 (3.1) Loss: For ML375: 2.7 (1.4) For MLAg250: 3.0 (1.6) At 3 years (223 and 226 women remaining for ML375 and MLAg250 respectively): A) ML375: 3.2 (1.8) MLAg250: 5.7 (2.4) B) ML375: 4.8 (2.1) MLAg250: 4.3 (1.9) C) ML375: 18.5 (3.7) MLAg250: 21.9 (3.8) D) ML375: 17.9 (3.8) MLAg250: 15.1 (3.5) E) ML375: 21.3 (3.8) MLAg250: 20.6 (3.8) Loss: For ML375: 5.1 (2.2) For MLAg250: 4.1 (2.0)**		**recruited for each arm was not specified**
WHO 1990[462] Study contained data from 3 RCTs conducted in 24 centres in 14 countries (mostly developing), but data only shown from	**2 multicentre RCTs**	**1++**	**2407**	**Women volunteers Exclusions: nulliparous, history of PID or pelvic abscess since last pregnancy, <6 weeks since parturition or abortion, history of ectopic pregnancy, recent STI, undiagnosed genital tract bleeding,**	**1: MLCu250 (n=1011) 2 : TCu380A (n=1396)**	**1: TCu220* (n=1032) 2: TCu220* (n=1396) ** Data not shown for this device***	**3 years for the ML250 5 years for the TCu380A**	**Cumulative discontinuation rates per 100 women (SE) at 3 years for both devices, and at 5 years for the TCu380A only, due to: A) Intrauterine pregnancy B) Ectopic C) Expulsion**	**At 3 years: A) ML250: 2.8 (0.6) T380A: 0.9 (0.3) B) ML250: 0 T380A: 0.1 (0.1) C) ML250: 3.1 (0.6) T380A: 7.0 (0.7) D) ML250: 0 T380A: 0 E) ML250: 17.6 (1.4) T380A: 12.9 (1.0) Discontinuation rate:**	**Not stated**	**Computer generated random allocation by sealed envelopes in balanced in blocks of six or ten**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
first (9 centres) and second trial (13 centres); third trial did not include any devices currently licensed in the UK				**congenital genital tract malformation, known/suspected genital tract malignancy, multiple uterine fibromyomas associated with menstrual disorders, evidence of anaemia, and history of hytidaform mole in last pregnancy**				**D) Perforation E) Medical removal for bleeding or pain** **Discontinuation rates** **Loss to follow-up** **Complications during insertions (%):** **A) Failure**	**For ML250: 38.5 (1.6)** **For T380A: 32.2 (1.3)** **Loss:** **For ML250: 14.7 (1.2)** **For T380A: 10.2 (0.9)** **At 5 years (for T380A only):** **A) 1.4 (0.4)** **B) 0.1 (0.1)** **C) 8.2 (0.8)** **D) 0** **E) 18.5 (1.2)** **Discontinuation rate: 46.7 (1.4)** **Loss: 15.5 (1.1)** **During insertion:** **A) ML250: 0** **T380A: 0**		
Cox 2002[134] **UK**	**Multicentre observational**	**3**	**574**	**Parous women, aged 18 to 45 years, requesting intrauterine contraception in general practice and at family planning clinics** **Exclusions: nulliparous, second or subsequent fitting, IUD fitted as emergency contraception, pregnant at fitting, <6 weeks since last pregnancy, concomitant contraception**	**Nova T380**	**No comparison group**	**5 years**	**Cumulative discontinuation rates per 100 women (95% CI) at 1, 2, 3, 4, and 5 years:** **A) Pregnancy*** **B) Expulsion** **C) Perforation** **D) Medical removal for bleeding or pain** **E) PID**** **Discontinuation rate** **Loss to follow-up**	**At 1 year:** **A) 0.8 (0.2, 2.0)** **B) 6.0 (3.9, 8.1)** **C) 0 (0, 0)** **D) 10.3 (7.5, 13.1)** **E) 0.9 (0.2, 2.3)** **Discontinuation rate: 26.2** **Loss: 69 women** **At 2 years:** **A) 1.6 (0.7, 3.4)** **B) 8.6 (6.0, 11.2)** **C) 0 (0, 0)** **D) 16.2 (12.6, 19.7)** **E) 0.9 (0.2, 2.3)** **Discontinuation rate: 40.7** **Loss: 86 women**	**Leiras Oy and Schering Health (manufacturers of Nova T 380)**	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								**** two of these were ectopic*** ***** there were 10 cases of PID of which 6 IUDs were removed. 4 of 6 cases included here; other 2 cases recorded as removal due to pain***	**At 3 years:** **A) 2.0 (0.9, 4.0)** **B) 10.3 (7.4, 13.2)** **C) 0 (0, 0)** **D) 21.1 (17.0, 25.1)** **E) 0.9 (0.2, 2.3)** **Discontinuation rate: 53.0** **Loss: 99 women** **At 4 years:** **A) 2.0 (0.9, 4.0)** **B) 12.3 (9.0, 15.6)** **C) 0 (0, 0)** **D) 26.5 (21.9, 31.1)** **E) 0.9 (0.2, 2.3)** **Discontinuation rate: 62.5** **Loss: 108 women** **At 5 years:** **A) 2.0 (0.9, 4.0)** **B) 13.0 (9.5,16.4)** **C) 0 (0, 0)** **D) 29.6 (24.7, 34.5)** **E) 0.9 (0.2, 2.3)** **Discontinuation rate: 67.5** **Loss: 110 women**		
Batar 1999[135] **3 centres in Finland**	**Multicentre observational**	**3**	**400**	**Women volunteers, aged 18 to 45, with uteri of normal shape and size, relying solely on IUD as contraception** **Exclusions: nulliparous, irregular menstrual cycles, <6 weeks since last pregnancy, history of gonorrhoea, repeated**	**NovaT380**	**No comparison group**	**2 years**	**Cumulative discontinuation rates per 100 women (95% CI; Pearl rate) at 1 and 2 years due to:** **A) Pregnancy** **B) Expulsion** **C)Medical removal for bleeding** **D) Medical**	**At 1 year (341 women remaining):** **A) 0.5 (0.0, 1.3; 0.5)** **B) 1.6 (0.3, 2.8; 1.6)** **C) 4.7 (2.6, 6.4; 4.9)** **D) 1.3 (0.2, 2.5; 1.4)** **E) 1.1 (0.0, 2.2; 1.1)** **F) 0** **Discontinuation rate: 11 (7.9, 14.1; 11.7)** **At 2 years (259 women**	**Not stated**	**All insertions performed within 7 days of onset of menstruation**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				episodes of PID or a single episode within 3 months preceding IUD insertion, significant anaemia or severe dysmenorrhea, post partum endometritis or infected abortion within 3 months prior to fitting IUD, pregnancy or previous ectopic pregnancy, use of chronic corticosteroid therapy of any contraindication to IUD contraception				**removal for pain E) Planning pregnancy F) PID Discontinuation rate**	**remaining): A) 1.6 (0.2, 3.0; 0.7) B) 2.8 (1.1, 4.6; 1.5) C) 8.7 (5.8, 11.7; 4.6) D) 2.3 (0.7, 3.9; 1.2) E) 6.0 (3.5, 8.6; 3.0) F) 0 Discontinuation rate: 24.5 (20.2, 28.8; 13.8)**		
Rivera 1999[463] Cameroon, Chile, Egypt, El Salvador, Malaysia, Mexico, Nigeria, Pakistan, Peru, Philippines, Sri Lanka, Thailand, Turkey, and Venezuela	**Secondary data analysis**	**2**	**2748**	**Women, aged 18 to 40 years, who were randomised to use the TCu380A in a previous multicentre RCT**	**TCu380A**	**No comparison group**	**1 year**	**Cumulative discontinuation rates (95% CI) at 1 year due to: A) All reasons B) Expulsion C) Bleeding or pain D) Personal reasons Effect of age on discontinuation rates at 1 year: A) All reasons B) Expulsion C) Bleeding or pain D) Personal reasons Effect of parity**	**At 1 year (2427 women remaining): A) 13.3 (11.9, 14.6) B) 3.1 (2.4, 3.8) C) 4.5 (3.7, 5.4) D) 4.3 (3.4, 5.2) Effect of age: A) <20: 19.1 (12.7, 25.5) 20-24: 14.6 (12.1, 17.2) 25-29: 13.1 (10.6, 15.5) 30-34: 11.2 (8.3, 14.0) 35+: 10.8 (7.2, 14.5) B) <20: 8.2 (3.7, 12.6) 20-24: 3.2 (2.0, 4.5) 25-29: 3.0 (1.8, 4.2) 30-34: 2.3 (1.0, 3.6) 35+: 1.8 (0.2, 3.3) C) <20: 4.0 (0.5, 7.5) 20-24: 4.9 (3.3, 6.5) 25-29: 4.8 (3.2, 6.3) 30-34: 4.2 (2.3, 6.0)**	**Family Health international and the US Agency of International Development**	**The original RCT was conducted by Family Health International**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								on discontinuation rates at 1 year: **A) All reasons** **B) Expulsion** **C) Bleeding or pain** **D) Personal reasons**	**35+: 3.7 (1.4, 6.0)** **D) <20: 6.8 (2.5, 11.2)** **20-24: 5.7 (3.9, 7.5)** **25-29: 3.8 (2.4, 5.3)** **30-34: 3.2 (1.5, 4.8)** **35+: 2.6 (0.7, 4.4)** **Effect of parity:** **A) 1: 15.7 (13.0, 18.4)** **2-3: 11.4 (9.5, 13.3)** **4+: 13.9 (11.2, 16.7)** **B) 1: 3.9 (2.5, 5.4)** **2-3: 2.8 (1.8, 3.7)** **4+: 2.8 (1.5, 4.1)** **C) 1: 4.8 (3.2, 6.5)** **2-3: 4.1 (2.9, 5.3)** **4+: 4.9 (3.2, 6.6)** **D) 1: 6.2 (4.3, 8.2)** **2-3: 3.6 (2.4, 4.8)** **4+: 3.4 (1.9, 4.9)**		
Dennis 2001[464] **UK**	**Cross-sectional**	**3**	**215**	**All nulliparous (n=123) and parous (n=92) women using GyneFix from 1997 to 1998 in North Mersey NHS Trust, Liverpool*** **The device was offered to: nulliparous women asking for non-hormonal contraception; parous women who had experience previous IUD expulsion or pain; parous women who preferred a frameless device** **** n=26 women used***	**Case note review and postal questionnaire**** ***** 183 (85%)***	**No comparison group**		**A) Pain upon insertion** **B) Menstrual changes since insertion** **C) Removals**	**A) n=132 responders; 'very painful' = 42 (32%), 'more painful than expected but bearable' = 41 (31%), 'as expected' = 25 (19%), 'less painful than expected' = 17 (13%), 'painless' = 7 (5%)** **B) n=183 responders; 'periods become unmanageably heavy' = 15 (8%), 'heavier but manageable' = 82 (45%), 'inter-menstrual changes' = 35 (19%), 'pelvic pain/dysmenorrhoea' = 25 (14%)** **C) 48 known removals; 16 due to bleeding problems, 11 to conceive, 10 due to pain, 2 due to suspected PID (negative in both cases), 1**	**National Co-ordinating Unit for Clinical Audit in Family Planning**	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				GyneFix for emergency contraception; data for these women were not presented separately and therefore could not be excluded	***completed questionnaires***				**due to pregnancy (conception prior to insertion)**		
Dennis 2001[465] **UK**	**Cross-sectional**	**3**	**1000 insertions**	**First 1000 GyneFix insertions at a family planning clinic in Liverpool* from 1997 to 2000** **** as the unit of measure in this study was an insertion, it was possible for a woman to be included more than once (e.g., re-insertion)***	**Case note review**	**No comparison group**		**Number of insertions and expulsion by parity** **Of expulsions, number that occurred in first 3 months** **Number of abandoned insertions**	**Insertions:** **Parous: 201** **Nullip: 799** **Expulsions:** **Parous: 12** **Nullip: 64** **Of 76 expulsions, 47 occurred in first 3 months** **11 abandoned insertions due to pain or failure to anchor device or inability to pass uterine sound**	**Some devices received free of charge from Contrel (manufacturer)**	
Kirkkola 1999[466] **Finland**	**Cross-sectional**	**3**	**221**	**Randomly selected women, aged 18 to 50 years, from the Population Register Centre**	**Postal questionnaire (393 sent; 56% response rate after two reminder letters)**			**IUD use:** **A) Ever** **B) By age group** **C) Rated as the 'best'**	**A) Yes: 32/100 responders** **No: 68/100 responders** **B) 18 to 29 years: 8 women** **30 to 40 years: 25 women** **41 to 50 years: 65 women*** **C) 31/209 (14.8%) responders** **** proportion of IUD users was significantly greater in older than in younger age groups***	**Emil Aaltonen Foundation and the Medical Fund of Tampere University Hospital**	**Questionnaire also sent to a random selection of Finnish men (n=395) but this data is not included here as it is outside the scope of the guideline**
Bahamondes 1999[467] ***Brazil***	***RCT***	***1+***	***806***	***Women choosing the IUD as a contraceptive device*** ***Exclusions: Nulliparouos, history***	***TCu380A (n=806)***	***TCu380S* (n=762)*** **** Data not shown for***	***5 years***	***Cumulative discontinuation rates per 1000 women** (SE) at 1, 3 and 5 years due to:***	***At 1 year:*** ***A) 0.1 (0.1)*** ***B) 4.5 (0.8)*** ***C) 4.3 (0.8)*** ***Continuation rate: 88.0 (1.2)***	***Ortho Pharmaceutical Ltd in Canada donated***	***Computer generated random allocation in sealed opaque envelopes***

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				of PID		***this device***		***A) Pregnancy B) Expulsion C) Medical removal for bleeding or pain Continuation rate Loss to follow-up GDG: ** text states per 1000 women, but I suspect this is actually per 100 women***	***Loss: 18.9 At 3 years (447 women remaining): A) 1.3 (0.6) B) 8.7 (1.2) C) 13.6 (1.5) Continuation rate: 66.6 (1.9) Loss: 33.2 At 5 years (213 women remaining): A) 1.8 (0.7) B) 13.8 (2.3) C) 19.2 (1.9) Continuation rate: 53.3 (2.5) Loss: 39.8***	***IUDs***	***All insertions performed during the first 7 days of menstruation***
Kivijarvi 1983[468] Finland	**RCT**	**1-**	**400**	**Sexually active women requesting IUD contraception Exclusions: pelvic infection, suspected pregnancy, abnormal undiagnosed bleeding, uterine abnormalities**	**MLCu250 (n=200)**	**MLCu250Short (n=200)**	**1 year**	**Cumulative discontinuation rates per 100 women (SE) at 1 year due to: A) Pregnancy* B) Expulsion C) Perforation D) Medical removal for bleeding or pain E) Medical removal for PID F) Planning pregnancy Continuation rate Loss to follow-up (%) * *none were***	**At 1 year (133 and 147 women remaining for ML250 and ML250 short respectively): A) ML250: 0.7 (0.7) ML250 short: 2.4 (1.2) B) ML250: 11.4 (2.5) ML250 short: 8.3 (2.1) C) ML250: 0 ML250 short: 0 D) ML250: 4.7 (1.7) ML250 short: 8.8 (2.2) E) ML250: 0.7 (0.7) ML250 short: 0.6 (0.6) F) ML250: 0.8 (0.8) ML250 short: 1.8 (1.0) Continuation rate: For ML250: 77.0 (3.2) For ML250 short: 78.4 (3.0) Loss: For ML250: 6.7**	**Not stated**	**'Randomised numbers' used for device allocation IUDs inserted 3 to 10 days after onset of menstruation**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								ectopic	**For ML250 short: 4.6**		
UNDP 1997[123] Study contained data from 2 RCTs conducted in 24 centres in developing countries, but data only shown from first trial; second trial did not include any devices currently licensed in the UK	**Multicentre RCT**	**1++**	**1396**	**Women volunteers** **Exclusions: nulliparous, history of PID or pelvic abscess since last pregnancy, <6 weeks since parturition or abortion, history of ectopic pregnancy, recent STI, undiagnosed genital tract bleeding, known/suspected genital tract malignancy, multiple fibromyomas associated with menstrual disorders, evidence of anaemia, and history of hytidaform mole in last pregnancy**	**TCu380A (n=1396)**	**TCu220* (n=1396)** **** Data not shown for this device***	**12 years**	**Cumulative discontinuation rates per 100 women (SE) at 8, 10 and 12 years due to:** **A) Intrauterine pregnancy** **B) Ectopic** **C) Expulsion** **D) Medical removal** **E) Medical removal for bleeding or pain** **F) Medical removal for PID** **G) Perforation** **Continuation rate**	**At 8 years (356 women remaining):** **A) 1.9 (0.5)** **B) 0.4 (0.3)** **C) 10.6 (1.1)** **D) 29.1 (1.6)** **E) 25.3 (1.5)** **F) 0.8 (0.4)** **G) 0.0 (0.0)** **Continuation rate: 25.5 (1.2)** **At 10 years (245 women remaining):** **A) 1.9 (0.5)** **B) 0.4 (0.3)** **C) 11.2 (1.1)** **D) 35.2 (1.8)** **E) 30.9 (1.8)** **F) 1.1 (0.5)** **G) 0.0 (0.0)** **Continuation rate: 17.6 (1.0)** **At 12 years (172 women remaining):** **A) 1.9 (0.5)** **B) 0.4 (0.3)** **C) 12.5 (1.4)** **D) 40.2 (2.1)** **E) 35.5 (2.1)** **F) 1.1 (0.5)** **G) 0.0 (0.0)** **Continuation rate: 12.3 (0.9)**	**Not stated**	**Computer generated random allocation by sealed envelopes in blocks of ten**
Bratt 1988[469] **Norway**	**RCT**	**1-**	**398**	**Women accepted for IUD contraception**	**MLCu375 (n=198)**	**MLCu250 (n=200)**	**3 years**	**Cumulative discontinuation rates per 100 women (SE) at 1, 2 and 3 years due to:**	**At 1 year:** **A) ML375: 1.1 (0.8)** **ML250: 0.5 (0.5)** **B) ML375: 4.3 (1.5)** **ML250: 2.6 (1.2)** **C) ML375: 9.6 (2.1)**	**Not stated**	**Study contained data on a third device which was not included as it is not currently**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								A) Pregnancy **B) Expulsion** **C) Medical removal for bleeding or pain** **D) PID** **Pearl index for unintended pregnancy** **Discontinuation rate**	**ML250: 3.6 (1.3)*** **D) ML375: 1.6 (0.9)** **ML250: 0.5 (0.5)** **Pearl index for unintended pregnancy:** **For ML375: 1.1** **For ML250: 0.5** **Discontinuation rate:** **For ML375: 16.7** **For ML250: 11.5** **At 2 years:** **A) ML375: 2.4 (1.2)** **ML250: 1.8 (1.0)** **B) ML375: 4.3 (1.5)** **ML250: 3.2 (1.3)** **C) ML375: 15.2 (2.7)** **ML250: 9.0 (2.2)** **D) ML375: 2.3 (1.1)** **ML250: 1.2 (0.8)** **Pearl index for unintended pregnancy: not specified** **Discontinuation rate:** **For ML375: 29.5** **For ML250: 29.6** **At 3 years:** **A) ML375: 2.4(1.2)** **ML250: 2.6 (1.3)** **B) ML375: 4.3 (1.5)** **ML250: 4.0 (1.5)** **C) ML375: 21.2 (3.2)** **ML250: 14.5 (2.8)** **D) ML375: 3.0 (1.3)** **ML250: 1.9 (1.1)** **Pearl index for unintended pregnancy:** **For ML375: 0.9**		**licensed in the UK** **Method of random allocation not specified**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									For ML250: 0.8 **Discontinuation rate:** **For ML375: 42.2** **For ML250: 41.8** **** difference between the two devices significant at p<0.05***		
Milsom 1990[163] **Sweden**	**RCT**	**1-**	**34**	**Women attending obstetrics and gynaecology clinic for IUD insertion** **Exclusions: irregular menstrual cycles, <6 menstrual cycles since last pregnancy, abortion or cessation of lactation, <2 spontaneous menstrual cycles since use of hormonal or intrauterine contraception**	**MLCu250 (n=16)**	**MLCu375 (n=18)**	**1 year**	**Mean menstrual blood loss (ml) prior to insertion, and at 3, 6, and 12 months (SE)** **Duration of menstrual cycle (days) prior to and after insertion (SE)** **Mean haemoglobin (g/l), hematocrit (%), erythrocyte count (10^{12}/l), and ferritin (μg/l) levels prior to insertion and at 6 and 12 months (SE)**	**Blood loss prior to insertion:** **ML250: 54.4 (10.3)** **ML375: 56.9 (6.9)** **Blood loss at 3 months:*** **ML250: 86.4 (10.3)** **ML375: 81.1 (8.3)** **Blood loss at 6 months:*** **ML250: 80 (10)** **ML375: 85 (8)** **Blood loss at 12 months:*** **ML250: 83 (12)** **ML375: 85 (8)** **Duration prior to insertion:** **ML250: 5.1 (0.1)** **ML375: 4.8 (0.2)** **Duration after to insertion:**** **ML250: 6.5 (0.2)** **ML375: 5.7 (0.4)** **No differences in any haematological parameters prior to or after insertion** **No differences in any haematological parameters between the two devices** **** difference from blood loss prior to insertion significant***	**Hjamer Svensson Fund**	**Method of random allocation not specified**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									at p<0.01 for both devices; no difference between the two devices ***** difference from duration prior to insertion significant at p<0.01 for both devices; no difference between the two devices***		
Larrson 1993[164] **Sweden**	**RCT**	**1-**	**34**	**Women attending obstetrics and gynaecology clinic for IUD insertion** **Exclusions: irregular menstrual cycles, <6 menstrual cycles since last pregnancy, abortion or cessation of lactation, <2 spontaneous menstrual cycles since use of hormonal or intrauterine contraception**	**MLCu250 (n=16)**	**MLCu375 (n=18)**	**3 years**	**Mean menstrual blood loss (ml) prior to insertion and at 2 and 3 years (SE)** **Mean haemoglobin (g/l), hematocrit (%), erythrocyte count (10^{12}/l), and ferritin (µg/l) levels prior to insertion and at 2 and 3 years (SE)**	**Blood loss prior to insertion:*** **ML250: 55 (8)** **ML375: 59 (9)** **Blood loss at 2 years:**** **MLCu250: 85 (12)** **MLCu375: 88 (15)** **Blood loss at 3 years:**** **MLCu250: 81 (14)** **MLCu375: 82 (9)** **No differences in any haematological parameters prior to or after insertion** **No differences in any haematological parameters between the two devices** **** data only reported for the 25 women remaining at the end of 3 years (13 and 12 for ML250 and ML375 respectively)*** ***** difference from prior to insertion significant at p<0.01 for both devices; no difference between the two devices***	**Gothenburg Medical Society and the Hjamer Svensson Fund**	**A follow-up study of Milsom study[163]** **Method of random allocation not specified**
Merki-Feld 2000[185]	**Retrospective**	**3**	**156**	**All women who used LNG-IUD or ML375**	**MLCu375 (n=104)**	**LNG-IUD (n=52)**		**Number of women followed**	**Women included in final analysis:**	**Not stated**	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Switzerland				**IUD in a family planning clinic with no evidence of ALO at time of insertion**				**for at least 10 months (others not included in final analysis)** **Detection of ALOs using PAP stained cervical smears by length of IUD use (%)**	**MLCu375: 65** **LNG: 34** **Used for 10 to 12 months:** **ML375: 9 women, 1 ALO (8.3)** **LNG: 5 women, 0 ALO (0)** **Used for 13 to 24 months:** **ML375: 27 women, 5 ALOs (18.5)** **LNG: 14 women, 0 ALO (0)** **Used for 24 to 40 months:** **ML375: 26 women, 7 ALOs (27)** **LNG: 15 women, 1 ALO (6.7)** **Total number of ALOs significantly lower in LNG group (p=0.03)**		
Walsh 1998[193] **USA**	**Multicentre RCT**	**1+**	**1833**	**Women requesting IUD as contraception**	**CopperT380A + 500mg azithromycin before insertion (n=918)**	**CopperT380A + placebo before insertion (n=915)**	**90 days**	**PID cases**	**azithromycin group: 1** **placebo group: 1*** ***OR 1.0, 95% CI 0.06, 15.95**	**National Institute of Child Health and Human Development**	**Computer generated random allocation by sealed identical pill bottles in blocks of ten; triple masked**
Zorlu 1993[194] **Greece**	**RCT**	**1-**	**277**	**Women requesting IUD as contraception** **Exclusions: history of ectopic pregnancy, <3months since last pregnancy, active salpingitis, dysfunctional uterine bleeding, genital tract malformation, antibiotics within the**	**TCu380A + 200mg doxycycline before insertion and then for two days (n=140)**	**TCu380A + no treatment (n=137)**		**PID cases**	**Doxycycline group: 1** **Control group: 1*** **OR 0.98, 95% CI 0.06, 15.73**		**Method of random allocation not specified; no placebo used**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				last month, any organic pelvic disease							
Harrison-Woolrych 2003[197] **New Zealand**	**Multicentre observational**	**3**	**16159**	**17,469 insertions from 1991 to 2001**	**MLCu375**	**No comparison group**		**A) Perforation (per 1000 insertions)** **B) Perforation by insertions per doctor (per 1000 insertions)** **C) Time from insertion to diagnosis of perforation*** **** 1 unknown***	**A) 28 (1.56)** **B) 1-9 insertions: 11 (3.0)**** **10-49: 11 (1.3)** **50-99: 1 (0.4)** **100+: 5 (1.7)** **C) At time of insertion: 4** **Within 3 months: 7** **4 months to 1year: 3** **1 to 2 years: 7** **2 years+: 6** **** RR 2.3, 95% CI 0.99, 5.26 when compared with 10-49 group; RR 7.3, 95% CI 0.94, 56.3 when compared with 50-99 group; RR 1.8, 95% CI 0.63, 5.19 when compared with 100+ group**		
Bonacho 2002[470] **Spain**	**Observational**	**3**	**358**	**All nulliparous and parous women who had GyneFix inserted during the study period**	**GyneFix**	**No comparison group**	**Ongoing at time of publication**	**A) Intrauterine pregnancy** **B) Expulsion** **From expulsions:** **1) % detected by user** **2) % occurring in the first 3 months** **3) % requesting another implant** **Risk of removal by uterine position (adjusted for age)**	**A) n=2; 0.6% (95% CI 0.09, 2.2)** **B) n=24; 6.7% (95% CI 4.4, 9.9)** **Of the 24 expulsions:** **1) 41.6** **2) 87.5** **3) 62.5** **Increased risk of removal with uterus in retroflexion position (RR 2.66, 95% CI 1.09, 6.48) and intermediate position (RR 1.19, 95% CI 0.40, 3.53) when compared with anteflexion position**	**Not stated**	
Masters	**Observatio**	**3**	**200**	**Nulliparous (n=136)**	**GyneFix**	**No**	**1 year**	**Discontinuation**	**At 1 year (121 women**	**Not**	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
2002[471] **UK**	**nal**			**and parous (n=64) women fitted with GyneFix at a family planning clinic in London**		**comparison group**		**rate per 100 women (95% CI) at one year due to:** **A) Pregnancy** **B) Expulsion** **C) Medical removal for bleeding or pain** **Number removed due to planning pregnancy** **Complications during insertion (%):** **A) Perforation**	**remaining):** **A) 0** **B) 0.08 (0.05, 0.13)** **C) 0.09 (0.05, 0.14)** **Planning pregnancy: 3** **During insertion:** **A) 0.5**	**stated**	
Snowden 1982[472] **UK**	**Multicentre observational**	**3**	**803**	**Sexually active nulliparous (n=147) and parous (n=656) women of any age from 16 family planning clinics around of the country** **Exclusions: <6 weeks since last pregnancy, recent PID, endometrial disease, postpartum endometritis, uterine abnormality, pregnancy, abnormal Papanicolaou smear, Wilson's disease**	**MLCu250**	**No comparison group**	**2 years**	**Cumulative discontinuation rates per 100 women (95%CI), by parity, at 1 and 2 years due to:** **A) Pregnancy** **B) Expulsion** **C) Medical removal due to bleeding or pain** **Complications during insertion (%) by parity:** **A) Dilatation** **B) 'Difficulty'** **C) Failed** **D) Mild pain** **E) Moderate pain** **F) Severe pain**	**At 1 year:** **A) Nullip: 0 (0.0, 2.7)** **Parous: 1.7 (0.7, 3.3)** **B) Nullip: 6.6 (2.9, 12.9)** **Parous: 4.9 (3.1, 6.8)** **C) Nullip: 11.7 (5.8, 17.6)** **Parous: 10.3 (7.7, 13.0)** **At 2 years:** **A) Nullip: *** **Parous: 3.2 (1.5, 5.0)** **B) Nullip: *** **Parous: 6.4 (4.2, 8.5)** **C) Nullip: *** **Parous: 17.7 (14.0, 21.3)** **During insertions:** **A) Nullip: 40 (27.8)** **Parous: 100 (15.2)** **B) Nullip: 12 (8.3)** **Parous: 27 (4.1)** **C) Nullip: 2 (1.4)** **Parous: 1 (0.2)**	**Not stated**	**IUDs inserted anytime during the menstrual cycle**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									D) Nullip: 66 (45.8) **Parous: 228 (34.8)** **E) Nullip: 44 (2.8)** **Parous: 36 (5.5)** **F) Nullip: 5 (3.5)** **Parous: 4 (0.6)** **** could not be calculated due to insufficient numbers remaining***		
Martinez 2002[473] **Spain**	**Multicentre observational**	**3**	**1684**	**Nulliparous (n=314) and parous (n=1370) women requesting IUD contraception**	**GyneFix**	**No comparison group**	**1 year**	**Cumulative discontinuation rates (SE) per 100 women at 1 year due to:** **A) Pregnancy** **B) Expulsion** **C) Bleeding** **D) Pain** **E) Perforation** **Complications during insertion (%) by parity:** **A) Failed** **B) Perforation**	**At 1 year (1097 women remaining):** **A) 0.3 (0.2)** **B) 5.6 (0.7)** **C) 2.3 (0.5)** **D) 0.7 (0.3)** **E) 0.3 (0.2)** **During insertion:** **A) Parous: 13 (1.0)** **Nullip: 10 (3.2)** **B) Parous: 3 (0.2)** **Nullip: 0 (0)**	**Italfarmaco**	
Sivin 1991[173] Data from both developed and developing countries	**Secondary data analysis**	**2**	**Only stated in woman-years by device**	**Women from 42 RCTs on IUD use published between 1970 and 1990**	**Surface area 350 to 380mm^2 (TCu380 & MLCu375)**	**Surface area 220 to 300mm^2 (MLCu250)**	**2 years**	**A) Pregnancies per 1000 woman-years (SE)** **B) ectopic rate per 1000 woman-years (SE)**	**At 2 years:** **A) T380: 3.4 (0.6)** **ML375: 5.9 (1.5)** **ML250: 9.4 (1.5)** **B) T380: 0.2 (0.1)** **ML375: 0** **ML250: 0.4 (0.3)**	**Not stated**	
Tsanadis 2002[474] **Greece**	**Observational**	**3**	**200**	**Parous married women requesting IUD as contraception** **Exclusions: allergic reaction to copper,**	**MLCu250**	**No comparison group**	**36 months**	**PID cases**	**No cases diagnosed**	**Not stated**	**IUDs inserted on the last day of menstruation**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				history of previous ectopic pregnancy, history of STI, history of PID, genital tract malformation, blood clotting disorders							
Farley 1992[191] **Studies from Europe, Asia, Americas and Africa**	**Secondary data analysis**	**2**	**22908**	**Women were from 12 RCTs on IUD use** **Exclusions: nulliparous, history of STI in past 6 months, previous PID, genital tract malformation or malignant disease, hytidoform mole in previous pregnancy**	**Copper T 380A** **MLCu375** **MLCu250**	**No comparison group**	**Various**	**A) No. of insertions** **B) PID cases** **C) PID rate per 1000 women-years** **D)Risk ≤ 20 days after insertion** **E) Age < 25 years**	**A) CopperT: 2795** **ML375: 1060** **ML250: 971** **B) CopperT: 4** **ML375: 0** **ML250: 7** **C) CopperT: 0.59** **ML375: 0.00** **ML250: 3.26** **D) Adjusted RR 6.30 (3.42 to 1.6)** **E) Adjusted RR 2.45 (1.56 to 3.85)**	**WHO Special Programme fo Research, Development, and Research Training in Human Reproduction and G.D. Searle Company**	**Data was from**
Delbarge 2002[475] **Study site not specified although authors came from Belgium**	**Observational**	**3**	**128**	**Women who had their IUDs removed with the intention of becoming pregnant and were living in a stable relationship** **Exclusions: history of PID or pelvic abscess since last pregnancy, <6 weeks since parturition or abortion, history of ectopic pregnancy, recent STI,**	**GyneFix removal**	**No comparison group**	**2 years**	**Pregnancy rate at 12 months:** **A) by age** **B) by duration of IUD use** **C) by parity** **Cumulative pregnancy rate since time of removal** **Number of pregnancies by parity**	**A) <30 years: 90** **>30 years: 87** **B) <24 months: 86** **>24 months: 90** **C) Nullip: 100*** **Parous: 80** **Since time of removal:** **At 3months: 58** **At 6 months: 72** **At 1 year: 88** **At 2 years: 99** **By parity:** **Nullip: 36** **Parous: 83**	**Not stated**	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				undiagnosed genital tract bleeding, congenital genital tract malformation, known/suspected genital tract malignancy, multiple uterine fibromyomas associated with menstrual disorders, evidence of anaemia, and history of hytidaform mole in last pregnancy					**** Nulliparous women conceived significantly earlier than parous women at p=0.007***		
Martin-Loeches 2003 [169] **Spain**	**Cohort study**	**2-**	**1073**	**71% nulliparous** **29% multiparous** **Aged 15-50 yeasrs**	**OC users (n=760)**	**IUD users (n=313)** MLCu375, Nova-T, Gine T380	**12 months**	**A) Modification of sexual desire** **Using the Female sexual function index** **B) High level of awareness of familuy planning** **C) Average relationship with partner** **D) Nulliparity** **E)Method in use for 6-12 months** **F) Increased age**	**No significant difference** **A) OR 1.32, (CI 0.70 to 2.49)** **In both groups** **Non-significant difference:** **B) Increased sexual desire** **OR 0.64 (0.41 to 1.01)** **C) Increased sexual desire** **OR 2.24 (1.36 to 3.69)** **D) Decreased sexual desire** **OR 1.57 (1.00 to 2.47)** **E)Greater sexual desire** **OR 0.41 (0.17 to 0.98)** **F) Decreased sexual desire** **OR 1.57 (1.00 to 2.47)** **1.05 (1.01 to 1.10)**	**Not stated**	**Uneven group size**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Hubacher 2001 [205] **Mexoico**	**Case-control**	**2-**	**1895**	**Women aged 18 and over**	**Exposure to copper IUDs**	**Infertile women with tubal occlusion (n=358)** **Infertile controls (n=953)** **Pregnant controls (n=584)**		**Risk of tuabl infertility**	**Tubal occlusion vs infertile controls: OR 1.0 (0.6 to 1.7)** **Tubal occlusion vs pregnant controls OR 0.9 (0.5 to 1.6)**	**USAID**	
Chi 1990 [476]	**Secondary analysis of a UK study**	**2-**	**5520**	**Parous women with CuIUD inserted by ob/gyn; women with uterine anatomical abnormalities excluded TCu200, TCu380A, MLCu250, ML375 5603 insertions performed between 1977-1987 at 23 international centres; 83 women had no data on position**		**Ante (n= 3135) Mid-pos.(n = 852) Retro(n = 1533)**		**Cumulative removasl rate per 100 insertions due to A) Pregnancy B) Expulsion C) Bleeding/pain D) total method-related discontinuation rate**	**At 6 months A) Anteverted: 0.6 ± 0.1 Mid-positioned: 0.4 ± 0.2 Retroverted: 0.7± 0.2** **B) Anteverted: 2.7 ± 0.3 Mid-positioned: 1.7 ± 0.5 Retroverted: 2.5± 0.4** **C) Anteverted: 2.1 ± 0.3 Mid-positioned: 2.3 ± 0.5 Retroverted: 2.6± 0.4** **D) Anteverted: 5.8± 0.4 Mid-positioned: 5.3 ± 0.8 Retroverted: 6.0± 0.6** **At 12 months A) Anteverted: 0.9 ± 0.2 Mid-positioned: 0.7 ± 0.3 Retroverted: 0.9± 0.3** **B)**	**Not stated**	**Derived from FHI RCT multi-centre IUD dataset**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									Anteverted: 3.5 ± 0.3 **Mid-positioned: 2.2± 0.5** **Retroverted: 3.5± 0.5** **C) Significant:** **Anteverted: 3.5 ± 0.4** **Mid-positioned: 6.3 ± 0.9** **Retroverted: 4.2± 0.6** **D)** **Anteverted: 8.5 ± 0.5** **Mid-positioned: 10.0 ± 1.1** **Retroverted: 9.2± 0.8**		
Avecilla-Palau et al (2003) [477] **Spain**	**Nested case-control**	**2-**	**355**	**Women of reproductive age attending a family planning centre in Barcelona between 1981-1999**		**IUD users diagnosed with pregnancy, miscarriage, abortion, ectopic pregnancy, birth (n=71)**	**IUD users during the same period who did not become pregnant (n=284)**	**Risk of pregnancy** **A) Anteverted** **B) Retroverted/mid-position** **Copper surface**	**A) OR 1.0 (reference)** **B) Adjusted OR 0.9 (1.0 to 1.7).** **>300mm vs <300mm vs >300mm: OR 1.0 (reference)** **Adjusted OR 2.6 (1.1 to 5.9)**	**none**	**Additional outcomes were: parity, hysterometry, copper surface of IUD**
Reinpraynoon 1998 [222] **Family Planning Clinic, Bangkok, Thailand**	**Non-comparative**	**3**		**Fifty women inserted with a TCu380A IUD after 40 years of age and used the device at least 36 months; women had no contraindications to CuIUD use**	**TCu380A**			**Side-effects reported during 36 months of follow-up** **A) Dysmenorrhea** **B) Intermenstrual pelvic pain** **C) Intermenstrual bleeding** **D) Inflammation/infection**	**Number (95%CI)** **A) 7 (5.8-26.7)** **B) 9 (8.6-31.4)** **C) 15 (17.9-44.6)** **D) 2 (0.4-13.7)** **No pregnancies, cases of PID, or expulsions occurred during the study period**		
Faundes	**Cohort**	**2-**	**481**	**women with T**		**Women**	**Women**	**position of the**	**No correlation**		**A secondary**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
1997 [162] **Brazil**				**shaped CuIUDs for at least 6 months** (T-Cu 200 or T-Cu 380)		**with no complaints (n=245)**	**with complaints (n=236)**	**TCu as imaged by vaginal USS**			**analysis [478] of this data suggests that position is influenced by growth and thinning of endometrium**
Sinei 1998 [231] **Kenya**		**2+**	**649**	**Women aged 20-30 years attending family planning clinics**	**T380A CuIUDs**	**HIV infected women (n=156)**	**HIV non-infected women (n=493)**	**Complications 1 months after insertion:** **A) Overall** **B) Infection-related complications** **C) IUD complaints** **D) PID** **E) Removal (pain, bleeding)** **F) Expulsions**	**OR (95%CI)** **A) 0.80 (0.38-1.68)*** **B) 1.02 (0.46-2.27)** **C) 1.41 (0.88-2.25)** ***Adj. for previous IUD use, study site, marital status, ethnic origin** **D) 1.4% vs 0.2%** **E) 4.2% vs 3.8%** **F) 2.1% vs 3.6%**		**For each HIV positive woman, 3 non-infected women were randomly recruited; longitudinal cohort; physicians were masked to HIV status Comparisons limited to 615 women with follow-up data: HIV infected women more likely to be single, in polygamous marriage, have more than one sexual partner (p<0.05)**
Morrison 2001 [232] **Kenya**	**Follow-up prospective cohort study from Sinei 1998 [231]** **24 months**	**2+**		**649 women requesting IUD and met eligibility criteria**	**See Sinei 1998 [231]**			**A) Overall complications(PID, IUCD removals,expulsions and pregnancy)** **B) Infection-related PID**	**A)** **HIV+ve: 14.7%** **HIV-ve: 14.8%** **Adjusted HR 0.98 (0.59-1.60)** **B)** **< 155 days** **Adjusted HR 1.84 (0.77-4.39)**		**T380A CuIUDs inserted in all patients; 94 women returned for follow-up**

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5 **Chapter 6 Progestogen-only intrauterine system: pregnancy rates, discontinuation rates, acceptability and**
6 **side-effects**

Bibliographic reference [1]	Study type [2]	Evidence level [3]	Number of patients [4]	Patient characteristics [5]	Intervention [6]	Comparison [7]	Length of follow-up [8]	Outcome measures [9]	Effect size [10]	Source of funding [11]	Additional comments [12]
Sivin 1994[141] **associated references:**[142-146] **Multinational** **Singapore** **Brazil** **Egypt** **USA**	**RCT**	**1-**	**2246**	**Parous women aged 18 to 38 in good health**	**LNG-IUS (n=1124)**	**CuT 380Ag IUD (n=1121)**	**7 years**	**Pregnancy rates per 100 women** **Discontinuation rate per 100 women**	**No significant difference at 7 years: LNG-IUS: 1.1 ± 0. CuT 380Ag: 1.4 ± 0.4** **Significant difference at 7 years: 77.2 vs 72.8**	**US Agency for International Development, UN Funds for Population Activities (UNFPA) Rockefeller Foundation etc**	

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
								Discontinuation due to **Bleeding problems:** **Amenorrhoea** **Menorrhagia** **Expulsion** **Headache/migraines** **Weight gain** **Dysmenorrhoea and spotting** **Weight loss** **Acne** **Missing thread** **Peforation**	**Significant difference at 7 years:** **5.9 vs 3.0** **4.4. vs 0.1** **0.7 vs 2.0** **2.9 vs 1.8** **0.6 vs 0.1** **0.7 vs 0.4** **No significant difference at 7 years:** **0.1 vs 0.2** **<0.1 vs 0.1** **0.1 vs 0.0** **0.1 vs 0.1** **cervical: 0.0 vs <0.1** **uterine: 0.1 vs 0.0**		

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
								Adverse effects: **Amenorrhoea** **Menorrhagia** **Dysmenorrhoea** **Depression** **frigidity** **Aneamia** **Ectopic pregnancy** **PID** **Vaginal lesions** **Actinomyces-like organisms** **Return of fertility:** **Pregnancy rate**	**Significant difference at 7 years:** **RR 2.15 (95% CI 1.31 to 3.56) at 3 months** **RR 7.24 (95% CI 4.14 to 12.65) at 3 years** **5.0 vs 8.0** **1.3 vs 3.3** **1.2 vs 1.1** **0.4 vs 0.4** **0.4 vs 0.8** **0 vs 2 at 7 years** **0.7 vs 0.7** **Significant difference:** **5.3 vs 7.7** **No significant difference:** **0.0 vs 0.1** **Follow- up of 110 women after removal** **96.4% vs 91.1% at 1 year**		

Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Luukkainen 1987 [147] **Associated references:** [148-150;153;154] **Finland and Brazil**	**RCT**	**1+**	**415**	**Healthy women Aged 18-40 No history of ectopic pregnancy**	**LNG-IUS 20µg/d (n=141)**	**IUD Nova T (n=134) LNG-IUS 30µg/d (n=140)**	**5 years**	**Discontinuation due to: Pregnancy Expulsion Bleeding & pain Amenorrhoea Rest hormonal side effects Infection Other medical Other personal Total Return to fertility**	**IUS IUD 1 7 2 7 11 21 15 0 11 2 1 4 4 2 18 19 63 62 No significant difference: Pregnancy rate after removal 79.1% vs 71.2% at 1 year 86.6% vs 79.7% at 2 years**	**International committee for Contraception Research of the Population Council, NY; Ford Foundation; International Development Centre of Canada; US Agency for International Development; Geo J Hecht Fund**	**Study population overlapped with** [209]

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Pakarinen 1996 [209] **Denmark, Finland, Hungary, Norway and Sweden**	**RCT**	**1+**	**438**	**Healthy women Requesting contraception after elective termination of pregnancy No anaemia No history of ectopic pregnancy**	**LNG-IUS 20µg/d (n=305)**	**IUD Nova T (n=133)**	**5 years**	**Discontinuation due to: Pregnancy Expulsion Bleeding Pain Amenorrhoea Rest hormonal side effects PID Other medical**	**Post-abortion IUS% IUD% p-value 0.8 9.5 0.0004 10.5 15.4 0.3785 13.7 22.6 0.1163 5.5 10.8 0.4387 2.1 0 0.1594 15.9 3.9 0.0054 0.7 2.3 0.3402 14.8 25.4 0.1233**	**Nil stated**	**Study population overlapped with** [147]

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Andersson [152] **Associated references: [151;153]** **Multinational Europe**	**RCT**	**1+**	**2758**	**Healthy women** **Aged 18-38 years** **History of at least one previous pregnancy** **No history of ectopic pregnancy** **No on-going breast-feeding** **No history of using injectable contraception during the preceding 12 months.**	**LNG-IUS 20µg/d (n=1821)**	**NovaT (n=937)**	**5 years**	**Continuation rates at 60 months:** **Contraceptive Efficacy (cumulative pregnancy rate at 5 years):** **Pregnancy rate:** **Ectopic pregnancies:** **Explusions at 60 month cumulative gross rate:** **Bleeding problems (removals due):** **Amenorrhea for at least 90 days during the first year of use:**	**NovaT – 315/937** **LNG-IUS – 736/1821** **NovaT – 5.9** **LNG-IUS – 0.5** **NovaT – 35** **LNG-IUS – 5** **NovaT – 7** **LNG-IUS – 5** **NovaT – 6.7** **LNG-IUS – 5.8** **NovaT – 20.7** **LNG-IUS – 13.7** **(with p,0.01 at five years).** **NovaT – 2.7% users** **LNG-IUS – 16.8% of users** **No difference between the groups.** **NovaT – 2.2** **LNG-IUS 0.8** **(with p<0.05)** **NovaT – 61.9 to 64.4** **LNG-IUS – 62.0 to 64.4** **NovaT – 1.6g/L increase** **LNG-IUS – 2.6g/L**	**Leiras Oy, Turku, Finland and from the Hjalmar Svensson Foundation (University of Goteborg), Sweden.**	**Reviewed in [125]**

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
								Pain: **Pelvic infections (60 month gross removal rates):** **Weight (start weight to weight at five years)** **Haemoglobin concentration after 5 years:** **Reported side effects:** **Menstrual problems:**	**increase** **NovaT – 25.9%** **LNG-IUS – 15.1%** **NovaT – 18.8% of users** **LNG-IUS – 6.3% of users**		
Cox 2002 [241] **Multicentre UK**	**Non-comparative**		**678**	**LNG-IUS users**	**LNG-IUS**	**NA**	**5 years**	**Cumulative discontinuation rates per 100 women (95% CI) at 1, 2, 3, 4, and 5 years:** **A) Pregnancy*** **B) Expulsion** **C) Perforation** **D) Medical removal for bleeding** **E) Medical removal for pain** **F) PID**	**At 1 year** **A) 0.6 (0.1 to 1.6)** **B) 4.5 (2.8 to 6.2)** **C) 0** **D) 10.5 (8.0 to 13.1)** **E) 2.3 (1.0 to 3.5)** **F) 0.9 (0.3 to 2.0)** **Discontinuation rate:** **30%** **At 2 years** **A) 1.0 (0.3 to 2.4)** **B) 5.2 (3.3 to 7.0)** **C) 0** **D) 12.6 (9.8 to 15.4)** **E) 3.5 (1.9 to 5.2)** **F) 1.2 (0.4 to 2.5)**		**Loss to follow up at 5 years (n=96)**

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
									Discontinuation rate: **43%** **At 3 years:** **A) 1.0 (0.3 to 2.4)** **B) 5.5 (3.6 to 7.4)** **C) 0** **D) 13.7 (10.8 to 16.7)** **E) 3.5 (1.9 to 5.2)** **F) 1.2 (0.4 to 2.5)** **Discontinuation rate:** **51%** **At 4 years:** **A) 1.0 (0.3 to 2.4)** **B) 5.5 (3.6 to 7.4)** **C) 0** **D) 14.7 (11.6 to 17.8)** **E) 4.3 (2.4 to 6.2)** **F) 1.2 (0.4 to 2.5)** **Discontinuation rate: 56%** **At 5 years:** **A) 1.0 (0.3 to 2.4)** **B) 5.9 (3.9 to 7.9)** **C) 0** **D) 16.7 (13.3 to 20.0)** **E) 4.3 (2.4 to 6.2)** **F) 1.2 (0.4 to 2.5)** **Discontinuation rate: 60%**		

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Bibliographic reference	Study type	Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
									At 5 years: **Number of removal due to amenorrhoea (n=26)** **Weight gain (n=16)** **PMT (n=14)** **Mood changes/depression (n=13)** **Breast tenderness (n=12)** **Headaches (n=9)** **Acne (n=7)** **Loss of libido (n=5)**		
Sivin 1992[248] **Finland**	**Cohort**	**2-**	**372**	**Women who stopped contraceptives for planned pregnancy**	**LNG-IUS**	**CuT 380 Ag IUD** **Norplant**	**2 years**	**Return of fertility** **Pregnancy rates after cessation of use**	**88% vs 88% vs 87% higher in women < 30 years**	**Not stated**	

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Chapter 7 Progestogen-only Injectable contraceptives: pregnancy rates, discontinuation rates, side-effects

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Fakeye 1991 [479] Nigeria	Cohort	2+	362	Women aged 18 to 40 years who selected a contraceptive method from Norplant, COC, CuIUD and DMPA, or had undergone surgical sterilisation.	DMPA (n=22)	Norplant (n=50) COC (n=101) IUD (n=184) Surgical sterilisation (n=5)	1 year	Pregnancy Discontinuation rate Reasons for discontinuation	0 DMPA, 0 Norplant, 0 IUD, 2 OC. (Not reported for sterilised group). 53.3% DMPA, 6.3% Norplant, 22.1% IUD, 72.3% COC Expulsion: 5% IUD; menstrual problems 55% DMPA, 6.5% IUD, 4% Norplant; medical reasons 3% COC; planning pregnancy 4.3% IUD other personal 8% COC, 4% IUD.	Not stated. Norplant supplied by Family Health International, Research Triangle Park, North Carolina	The study was set up to establish the demographics of Norplant users and its acceptability vs other contraceptive methods. 57% of COC users, 1% IUD and 2% Norplant were lost to follow up. Woman months of use were 177 with DMPA, 521.5 Norplant, 1827 IUD, 487 COC.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
WHO 1983 [265] Multinational: Egypt Thailand Nigeria Pakistan Yugoslavia Luxumberg The Phillipines Mexico Italy Chile The Netherlands	RCT	1+	3172	Non-breastfeeding women choosing to use injectable contraception.	DMPA 150 mg by IM injection every 90 days (n=1587)	NET-EN 200 mg every 60 days for 6 months, then either every 60 days (n=789), or every 84 days (n=796)	2 years	Pregnancy (cumulative) Amenorrhoea (cumulative) Bleeding problems (cumulative) Discontinuation (cumulative) Reasons for discontinuation Blood pressure Weight	0.1% vs 0.4% NET-EN (60 day), vs 0.6% NET-EN (84 day) at 1 year; 0.4% vs 0.4% vs 1.4% at 2 years 11.9% vs 6.8% vs 8.4% at 1 year; 24.2% vs 14.7% vs 14.6% at 2 years 15.0% vs 13.6% vs 13.7% at 1 year; 18.8% vs 18.4% vs 21.8% at 2 years 51.4% vs 49.7% vs 50.3% at 1 year; 73.5% vs 70.7% vs 72.4% at 2 years Abdominal distension or discomfort 1.1/100 woman-years vs 0.6 vs 0.3; weight gain 2.1 vs 1.6 vs 0.8 kg/100 woman-years Systolic (mmHg) -3.0 vs -2.5 vs +0.1; diastolic -1.6 vs -1.8 vs -0.4 at 2 years +3.3 kg vs +3.3 vs +3.4 at 2 years	WHO	Study conducted in 12 centres, 9 in developing countries, and 4 in developed countries (Yugoslavia, Luxembourg, Italy, Netherlands). For amenorrhoea, differences between both NET-EN groups and DMPA significant. Discontinuation rate for abdominal distension or discomfort significantly lower in the NET-EN (84-day) group vs DMPA. First injection given in first 5 days of cycle.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
WHO 1977 [266] Alexandria Bahia-salvador Bangkok Bombay Chandigarh Ibadan Ljubljana Manila Utrecht	RCT, 10-centre, international	1+	1678	Healthy women aged 18-40 years of proven fertility (last delivery within past 5 years), with regular menstrual bleeding and any previous pregnancy completed more than 60 days before entry into the study.	DMPA 150 mg by IM injection into gluteal muscle every 12 weeks ± 5 days (n=846)	NET-EN 200 mg by IM injection into gluteal muscle every 12 weeks ± 5 days (n=832)	1 year	Pregnancy Discontinuation (non-medical reasons) Discontinuation (medical reasons) Discontinuation for amenorrhoea	0.7±0.4 vs 3.6±0.7/100 woman-years 7.7 vs 9.5/100 woman-years 23.4±1.7 vs 16.9±1.4/100 woman-years 11.5 vs 1.8/100 woman-years	WHO	First injection given in the first 5 days of cycle. Planned 2 years, terminated after approximately 1 year because pregnancy rate with NET-EN exceeded the previously allowable maximum of 2 pregnancies per 100 woman-years. Exposure was 398.5 vs 420.7 woman-years in the DMPA vs NET-EN groups. Of the 24 pregnancies that occurred in the NET-EN group, conception occurred in the first month in 18 cases, 13 of which were estimated to have occurred in the third month. Except for the discontinuation rate for non-medical reasons, all between-group differences were statistically significant

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Chinnatamby 1971 [267] Ceylon	Cohort	2+	1035	Women aged 20-44 years	DMPA 150 mg every 90 days by IM injection into gluteal muscle (n=515)	NET-EN 200 mg every 84 days by IM injection into gluteal muscle (n=520)	15 months	Pregnancy	0.4 vs 2.3/100 woman-years	Not stated	First injection given between days 4 and 7 of cycle. Results for menstrual patterns only reported for the whole group, not by intervention group. Follow-up for 5770 vs 4391 cycles in DMPA and NET-EN groups respectively.
O'Dell 1998 [268] USA	Cohort (retrospective)	2-	161	Postpartum inner-city adolescents aged 19 years or younger who returned to the hospital's family planning clinic within 14 weeks of discharge, and chose either DMPA or a OC within 6 weeks of delivery. Exclusions: those using condoms alone, no contraception, diaphragm, or Norplant.	DMPA every 12 weeks (n=111)	OC (n=50)		Reason for choosing method (n=80 DMPA, n=33 OC)	DMPA: 29% reluctant to use OC, 28% fear of pregnancy, 24% ease & convenience, 13% duration of action. OC: 47% fear of pregnancy, 22% reluctant to use DMPA, 13% reluctant to Norplant.	None stated	For adolescents returning for further DMPA injections between 12 and 14 weeks after the previous, the injection was only administered after a negative pregnancy test. Beyond 14 weeks, the injection was delayed until the next menstrual period.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Side effects (n=80 DMPA, n=33 OC)	At least one: 93% DMPA, 58% OC, p<0.001; weight gain 54% vs 30% p<0.05; irregular bleeding 49% vs 12% p<0.05, headache 39% vs 21%, fatigue 33% vs 9% p<0.05; mood changes 29% vs 9%, p<0.05; decreased libido 23% vs 0, p<0.05; hair loss 20% vs 6%; abdominal pain 20% vs 6%; acne 11% vs 0; breast tenderness 8% vs 3%; nausea 0 vs 5%.		Telephone interviews were conducted 12 to 18 months postpartum. These were completed by 80 (72%) of the DMPA group, and 37 (74%) of the OC group. Medical records were also reviewed for all girls up to the date of the interview.
								Continuation rate (life-table analysis)	At 6 months 58% (SE 5%) DMPA vs 45% (SE 7%)		Mean age of girls at delivery was 17.8 ± 1.4 years.
									At 12 months 34% (SE 5%) 32% (SE 7%)		46% of the DMPA group had previously used OC.
								Reasons for discontinuation (given by 39/55 DMPA users, 16/19 OC users)	Side effects 79% vs 44%; sexual inactivity 21% vs 13%, forgetting an injection/pill 13% vs 50%. DMPA users injection site pain (5%), OC users no refills (13%)		Median duration of use was 8.1 months DMPA vs 5.4 months OC.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Acceptability	100% DMPA vs 93% OC continuers, and 75% vs 79% discontinuers would recommend the method to their friend. 44% vs 73% discontinuers would used the methods again.		
								Pregnancy (cumulative)	11% DMPA (SE 3%) vs 28% (SE 7%) OC, p=0.003.		
Heber 1988 [480]	Case-series	3	627	Women from an Australian general practice who had used DMPA	DMPA	-	14,242 cycles	Pregnancy	1 in total (her DMPA was given 7 weeks postpartum)	Not stated	Age range of women was 15 to 51 years
								Reasons for discontinuation (n=500)	0.2% unplanned pregnancy, 1.2% acne, 14.6% unacceptable bleeding, 0.2% cramping, 2% depression, 2% weight gain, 2.2% loss of libido, 16% pregnancy desired, 11.8% moved or lost to follow up, 27% no further need, 11.4% prefer another method, 11.4% switched to another method.		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Templeman 2000 [277] USA	Cohort	2+	122	Postpartum adolescents aged under 18 years, enrolled before hospital discharge	DMPA 150 mg IM before hospital discharge (n=76)	OC (containing ethinylestradiol 30 to 35 microgram), starting 2 weeks after delivery date (n=46)	1 year	Discontinuation rate Reasons for discontinuation (given by 33% and 52% of DMPA vs OC discontinuers) Menstrual pattern	45% vs 73%, p=0.002 Nausea 0 vs 17%, disrupted menstrual cycles 40% vs 4%, forgot to take 0 vs 25%, multiple side effects 40% vs 25%, planning pregnancy 0 vs 8%, not sexually active 0 vs 13%, couldn't attend clinic 8% vs 0, weight gain 12% vs 0, ran our 0 vs 8% Normal 20.5% DMPA vs 50% OC, irregular 38% vs 23%, too frequent 6% vs 4%, prolonged 15% vs 9%, amenorrhoea 20.5% vs 14%.	Not stated	Pregnancy also reported in 13 adolescents, all of whom had discontinued contraception before becoming pregnant (3% DMPA vs 24% OC, RR for pregnancy with OC vs DMPA 9.09 (95% CI 2.1 to 39.2). Mean time to pregnancy was 17.1 (SE 0.4) vs 13.2 (SE 1.18) months with DMPA vs OC, p<0.001.
Colli 1999 [276] New Zealand	Cohort	2+	6262	Women already using one of three contraceptive methods (DMPA, IUD, OC).	DMPA (n=1721)	IUD (n=2072) OC (n=2469)	5 years	Discontinuation rate at 2 years	48% DMPA, 44% IUD, 42% OC	Not stated	Set up to investigate the risk of cervical dysplasia in users of contraception.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Reasons for discontinuation (per 100 woman-years)	Desire to conceive 6.6 vs 9.5 vs 13.1; preference 10.2, 4.7, 11.5; contraception not required 5.8 vs 1.6 vs 5.1; vasectomy 2.5 vs 2.6 vs 3.6; sterilization 2.9 vs 1.6 vs 2.1; weight problem 5.7 vs 0.1 vs 2.5; menorrhagia 1.5 vs 4.4 vs 1.8; noncompliance 2.1 vs 0.1 vs 4.2; intermenstrual bleeding 1.1 vs 1.0 vs 4.7; pelvic pain 0.4 vs 4.4 vs 0.9; headaches 0.6 vs 0.1 vs 3.8; pelvic infections 0.1 vs 3.4 vs 0.1; pregnancy whilst using method 0.3 vs 2.2 vs 2.5		Withdrawal rates from the study were 16.1% DMPA, 9.5% IUD, 10.5% OC. Mean duration of use was 866 days DMPA, 899 days IUD, 923 days OC. Due to the study population being existing users of the contraceptive methods, the discontinuation rates quoted at 2 years may not accurately reflect early discontinuation. Many women (number not stated) switched between the devices under investigation.
Harel 1996 [278] USA	Cross-sectional survey	3	66	Adolescents in US hospital clinic who had recently discontinued a long-acting contraceptive	DMPA (n=35)	Norplant (n=31)	After discontinuation 8.4±0.8 vs 8.2±1.0 months.	Satisfaction	48% vs 52% “somewhat”, 29% vs 35% dissatisfied, 73% vs 61% would recommend to a friend, 51% vs 39% would resume method	Partly supported by Maternal and Child Health Grant	DMPA: 15% stopped after 1 injection, 44% after 2, 23% after 3, 18% after 4 or more.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Reasons for discontinuation	60% vs 68% irregular bleeding, 40% vs 42% weight gain, 26% vs 35% increased headaches, 20% vs 42% mood changes, 20% vs 29% fatigue, 14% vs 19% breast tenderness, 14% vs 16% amenorrhoea, 20% vs 10% loss of scalp hair, 6% vs 19% painful administration site, 9% vs 10% acne.		Norplant removal rates 23% during year 1, 29% year 2, 48% year 3.
								Menstrual pattern after discontinuation	50% vs 81% resumed in first month, duration of bleeding 7.0±2.0 vs 5.0±2.5 days		Between-group differences in return of menses, and conception rate significant, p=0.01.
								BMI	Gains of 1.1±0.3 vs 1.3±0.6 from baseline during mean 9.2±0.9 vs 21.8±1.6 months of use		
								STI	20% vs 64% during use, 20% vs 32% after discontinuation		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Consistent condom use	28% vs 3% during use, 32% vs 20% after discontinuation		
								Abnormal Pap smears (atypia & squamous intraepithelial lesions)	26% vs 45% during use, 6% vs 10% after discontinuation		
								Pregnancy	20% vs 48% during follow-up		
Harel 1995 [481] USA	Cross-sectional survey	3	78	Adolescent users of DMPA. Hospital clinic setting	DMPA 150 mg every 3 months (n=36)	DMPA 150 mg every 6 weeks (n=27) DMPA 150mg every 3 months in previous COC user (n=15)	9 months	Reasons for choosing DMPA	Total population: convenience (46%), long-term protection (37%), problems with previous method (30%), desire not to have periods (17%), invisibility of method (17%), reliability (15%), cost (4%)	Partly supported by Maternal and Child Health Grant	Mean duration of COC use was 13.1±3.8. Previous contraception methods used were condoms (72%), COC (48%), Norplant (5%).
								Reasons for continued DMPA use	Total population: not having to take pill every day (54%), easier than previous method (16%), no periods (15%)		
								Satisfaction	52% vs 39% vs 87% very, 78% vs 84% vs 100% would recommend to a friend		

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Concerns regarding use	Total population: 81% not concerned about follow-up visits, 48% and 52% somewhat or very concerned by menstrual changes, and other side effects (not defined)		
								Concerns regarding use	Total population: 81% not concerned about follow-up visits, 48% and 52% somewhat or very concerned by menstrual changes, and other side effects (not defined)		
								Discontinuation rate	25% vs 19% vs 20%		
								Reasons for discontinuation	Most common: irregular bleeding (25%), weight gain (11%), amenorrhoea (8%), increased appetite (8%)		
								BMI	Gains of 1.08±0.29 vs 1.28±0.49 vs 1.05±0.73 from baseline at 6 months		
								Pregnancy	0		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Lei 1996 [283] China	Cohort	2+	421	Chinese women who chose to use DMPA, aged 18 to 40 years, used only DMPA during the study (condoms permitted to prevent transmission of sexually transmitted infections), had regular menstrual cycles during the previous 6 months.	DMPA users given structured counselling (a program detailing the mode of action of DMPA, common hormonal effects and side effects; watched a video of American women talking about use of DMPA, and given an information booklet) n=204	DMPA users given routine counselling (not given information about the expected side effects of DMPA unless asked). n=217	1 year	Discontinuation rate (cumulative)	11% structured vs 24% routine, p<0.0001	Not stated (correspondence address is Pharmacia & Upjohn)	DMPA administered into deltoid or gluteal muscle within the first five days of the menstrual cycle or before discharge from hospital postpartum / postabortion.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				investigational medication. Exclusions: current or history of thrombophlebitis, hypertension or vascular disease, active liver dysfunction or disease, significant neuroendocrine or pelvic abnormalities, known or suspected breast or genital organ malignancy, undiagnosed vaginal bleeding, known or suspected pregnancy, use of other				Reasons for discontinuation	All medical reasons 6% vs 26%, p<0.05 (irregular bleeding 5% vs 19%, amenorrhoea 0 vs 2%, 'other' 0.5% vs 5%) Missing injection 0.5% vs 4%, p<0.05, personal reasons 4% vs 9%, lost to follow up 0 vs 9%, protocol violation 1% vs 0%.		Centres that gave structured counselling were separated from those that gave routine counselling by the Yangtze river.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Canto de Cetina 2001 [69] Mexico	RCT	1+	350	Mexican women who chose to use DMPA (and only used this method), aged 18 to 35 years, living in a rural area, or proven fertility, having regular menstrual cycles in the previous 6 months, not breastfeeding.	DMPA users given structured counselling (detailing the mode of action of DMPA, common hormonal effects and side effects; stressing that bleeding irregularities not detrimental to health. Information repeated at each follow up visit). Women encouraged to return to the clinic if they had concerns about DMPA's effects on their health.	DMPA users given routine counselling ('routine information' about side effects, additional information provided is woman asked)	1 year	Discontinuation rate (cumulative) Reasons for discontinuation	17.1% structured vs 43.4% routine, p<0.05 Amenorrhoea 3% vs 17% p<0.05, irregular bleeding 3% vs 10% p<0.05, heavy bleeding 2% vs 5% p<0.05, weight gain 2% vs 2%, vomiting 1% vs 1%, dizziness 0.6% vs 0.6%, depression 1% vs 2%, loss of libido 1% vs 2%, planned pregnancy 1% vs 2%, lost to follow up 1% vs 2%.	None stated	DMPA administered within the first five days of the menstrual cycle. Method of randomisation not reported.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: abnormal PAP smears, current or history of thrombophlebitis, thromboembolic disorders, hypertension, cerebral vascular disease, active or chronic liver disease, known or suspected breast or genital organ malignancy, endocrinopathy undiagnosed, vaginal bleeding, diabetes mellitus.							

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Chapter 7 – Progestogen only injectable contraceptives: Management of bleeding problems

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Sapire 1991 [282] South Africa	Cohort	2-	653	Women in the puerperium (within 6-12 hours of delivery)	DMPA every 3 months (dose not stated) (n=349)	NET-EN every 2 months (dose not stated) (n=304)	6 months (2 vs 3 injection intervals for DMPA vs NET-EN)	Mean duration of bleeding Incidence of prolonged bleeding (>21 days)	35.9 (SD 31.55) vs 33.2 (SD 20.58) days 21% vs 25.5% in the first injection interval; 12.7% vs 12.9% in the second	Berlimed and Upjohn provided 'support'	Women who bled for more than 10 days were given 5 days treatment with naproxen 250 mg three times a day, or tranexamic acid 1.5 grams/day. It was reported that the mean number of days before bleeding stopped after both treatments was 4.69 and 4.96 days. To determine whether treatment was effective, a placebo-controlled double-blind study comparing naproxen with placebo was conducted in a subgroup of the total population (n=48). Details of the methods of this study were not given. Duration of was not significantly different with naproxen vs placebo.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Said 1996 [279] Egypt, Thailand, Indonesia, Pakistan, Philippines	RCT (6 centres)	1+	1035 (n=278 were randomised to treatment)	Women aged 18 to 40 years attending a family planning clinic for contraception and willing to start 150 mg DMPA every 3 months. Those who had a vaginal bleeding episode lasting more than 7 days during their first or second injection interval (first 6 months of treatmet) and who wished to be treated were randomised to a 14-day course of oestrogen or placebo.	50 microgram ethinylestradiol daily (n=90) or 2.5 mg piperazine oestrone sulphate(n=91)	Placebo (n=97)	1 year	Success of treatment (vaginal bleeding stopped for 2 days or more during treatment and had not recurred)	93% ethinylestradiol vs 76% oestrone vs 74% placebo (p<0.001 ethinylestradiol vs oestrone or placebo)	WHO	Method of randomisation not reported. Study reported to be double-blind. If the oestrogen/placebo treatment failed, the investigator was free to give a second treatment of his/her choice. 45 women received treatment with a COC (n=15), oestradiol cypionate (n=6), conjugated oestrogens (n=2), haemostatic agents (n=4),

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: Pregnancy or lactation in past 6 months, diabetes, history of thromboembolism, hypertension, recent or severe liver disease, a Papanicolaou smear grade 3 or above, vaginal bleeding of unknown aetiology, abnormal discharge from nipples, malignancy, use of barbiturates, anti-convulsants, rifampicin, systemic corticosteroids, dugs affecting the cardiovascular or hepatic systems, any drug used on long-term basis, OC in last 6 months, any injectable contraceptive in last 12 months.				Median number of bleeding / spotting days Median number of bleeding days	5 vs 9 vs 9 days 2 vs 2 vs 3 days		non-steroidal anti-inflammatory agents (n=4), iron, calcium, vitamins, and/or diazepam (n=14). Their outcomes were not reported separately.

Chapter 7 – Progestogen only injectable contraceptives: return to fertility

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Affandi 1987 [335] Indonesia	Cohort	2	173	Ex-contraceptive users	Norplant (n=51)	Lippes IUD (n=75) and DMPA (n=47)	2 years	Cumulative pregnancy rate after discontinuation	Norplant vs DMPA: 76.5% vs 70.2% at 1 year (RR 1.09, 95% CI 0.86 to 1.39) 90.2% vs 89.4% at 2 years (RR 1.01, 95% CI 0.88 to 1.15)	Not stated	
Garza-Flores 1985 [333] Mexico	Cohort	2-	24	Mexican women who had voluntarily discontinued DMPA or NET-EN. All women admitted to the study 90 days after the last injection.	DMPA 150 mg every 90 ± 7 days (n=14)	NET-EN 200 mg every 60 ± 7 days for the first six months, and every 84 ± 7 days thereafter (n=10)	1 year	Return to ovulation (serum progesterone concentration above 5 nanogram/ml) (n=10 DMPA, n=6 NET-EN)	5.5 ± 1.9 months DMPA vs 2.6 ± 1.7 months NET-EN, p<0.001	WHO	Mean duration of use 2.9 ± 1.2 years DMPA vs 3.2 ± 1.6 years NET-EN (minimum 1.2 years both groups).

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Pardthaisong 1980 [334] Thailand	Cohort	2-	796	Thai women who stopped using their contraceptive method to have a planned pregnancy.	Past DMPA users (n=796)	Past IUD users (n=125)	2 years	Time to conception (estimated, median) Cumulative conception rates (± SE)	5.5 months DMPA (+ 15 weeks estimated duration of effect of last injection) DMPA vs 4.5 months IUD. 78.2% ± 1.5 vs 79.0% ± 4.4 at 1 year 92.1% ± 1.1 vs 93.3% ± 3.0 at 2 years	WHO	Investigators assumed that DMPA has a duration of effect of 15 weeks after an injection, and the contraceptive effects of the IUD ceased as soon as the device was removed. Date of conception estimated from the date of birth after a full term gestation; or from the date of the last menstrual period for other pregnancies. Mean ages were 24.5 ± 3.8 years DMPA vs 27.7 ± 5.1 years IUD; mean number of pregnancies 1.5 ± 1.4 vs 2.0 ± 1.6; proportions never pregnant were 4.4% vs 0 ($p<0.05$ for all differences between groups). Duration of DMPA or IUD use not reported.

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2 **Chapter 7 – Progestogen only injectable contraceptives: weight changes**
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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Espey 2000[482] India	Cohort	2+	306	Women of the Najavo tribe in India, aged 18 to 40 years who completed 5 consecutive injections at intervals of 10 to 14 weeks, and had weights recorded at 1 year and/or 2 year intervals. Those with incomplete records, or diabetes or thyroid disease were excluded.	DMPA (dose not stated) (n=172 [115 interval, 57 postpartum])	Non-progestin hormonal method, or non-hormonal method (n=134 [94 interval, 40 postpartum])	2 years	Weight	Mean gain of 4.2 vs 1.4 kg at 1 year, and 7.2 vs 1.8 kg at 2 years in the interval groups (n=219), and gain of 3.2 vs 0.6 kg at 1 year, and 6.5 vs 1.6 kg at 2 years in the postpartum groups (n=97).	Not stated	'Interval' DMPA group were those at least 20 weeks beyond a pregnancy of at least 20 weeks gestation at the time of the first DMPA injection. 'Postpartum' women were those given DMPA within 5 to 8 weeks of delivering a singleton pregnancy of at least 20 week gestation. Weight changes were adjusted to account for baseline differences in age, parity and weight. Differences between DMPA users and nonusers were significant before and after adjustment.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Mohllajee 2004[285]	Systematic review	2++	3 studies (all evaluating DMPA) (n=1315)	Overweight women using progestogen-only contraception	DMPA (in obese or overweight women)	DMPA (in 'normal' weight women), and in 1 study, overweight OC users	1 year in OC controlled study; 9 months in menstrual disturbances study	Weight changes (2 studies) Menstrual disturbances (1 study)	Significantly greater weight gain of 6.2 vs 3.1 vs 3.4 kg in overweight (BMI > 8th percentile for their age) DMPA users vs 'normal' weight DMPA users vs overweight OC users in 1 study. Similar weight gain in overweight (>91 kg) DMPA users vs total group of DMPA users in 1 study (mean 2.0 vs 1.9 kg). No significant differences in the incidence of increased or excessive menstrual bleeding between obese (BMI ≥ 30 kg/m^2), overweight (BMI 25 to 29.9 kg/m^2), and non-obese (BMI < 25kg/m^2) DMPA users.	WHO (not stated for original studies)	Quality of studies 'very poor'. Neither of the two studies evaluating weight gain adjusted for confounders and did not define obesity in the same way as WHO medical eligibility criteria (BMI ≥ 30kg/m^2)

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Hameed 2001[483] Pakistan	Cohort	2-	100	Healthy women attending family planning clinics for contraceptive advice	OC (n=50) DMPA 150 mg IM every 3 months(n=25) NET-EN 100 mg/ml IM (n=25)	Women acted as own controls (prior to using contraceptive)	3 to 6 months	Weight changes Blood pressure	Mean weight gain vs baseline of 1.7 vs 2.2 vs 2.3 kg in OC vs DMPA vs NET-EN at 6 months Systolic: mean increases of 5.2 vs 4.5 vs 4.5 mmHg; Diastolic: mean increases of 2.2 vs 4.1 vs 3.6 mmHg	Not stated	No between-group analysis reported. Sodium, potassium, chloride and bicarbonate concentrations also recorded. All reported changes in all groups statistically significant from baseline.

Chapter 7 – Progestogen only injectable contraceptives: depression

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Civic 2000[286] USA	Cohort	2+	457	Women enrolled in a population-based study of effects of DMPA on bone density, aged 18 to 39 years	DMPA (n=183)	Nonusers of DMPA (n=274)	3 years	Depressive symptoms	Reported by 28% DMPA users vs 18% nonusers at baseline; 21% DMPA users vs 36% in DMPA discontinuers vs 14% nonusers at month 6; 21% vs 22% vs 14% at month 12; 16% vs 19% vs 15% at month 18; 21% vs 28% vs 16% at month 24; 18% vs 25% vs 14% at month 30; 8% vs 21% vs 12% at month 36. OR 1.44; 95%CI 1.00 to 2.07 in continuous DMPA users vs non users.	National Institute of Child Health and Human Development, National Institutes for Health	113 (62%) discontinued DMPA use. 31% and 20% of DMPA users vs nonusers were lost to follow-up. Depressive symptoms subsided at visits subsequent to discontinuation relative to nonusers. Nonusers of DMPA were selected randomly. Women completed questionnaires every 6 months, which included a 10-item version of the Community Epidemiology Survey-Depression Scale.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									OR 1.60; 95%CI 1.03 to 2.48 in discontinuers vs non users, and OR 2.30; 95%CI 1.42 to 3.70 at visit prior to discontinuation, and OR 2.46; 95%CI 1.46 to 4.14 at visit immediately after discontinuation. DMPA discontinuers more likely to report depressive symptoms at baseline (35% vs 17%).		
Gupta 2001[287] USA	Cohort	2-	63	Female adolescents aged between 15 and 21 years who chose DMPA as their contraceptive method.	DMPA users (n=39)	Non users of hormonal contraception (should not have used DMPA for past 6 months) (n=24)	1 year	Change in BDI scores from baseline	-5.1 (SD 7.8) DMPA (p=0.01 from baseline) vs +0.3 (SD 4.2) control	(Partly) by a New England Medical Center Research Funds grant	Participants completed Beck Depression Inventory (BDI) scale and the Multiple Affect Adjective Checklist-Revised (MAACL-R) questionnaires every 3 months.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: chronic illness, physical disabilities, past history of psychiatric illness requiring hospitalisation or psychotropic medication. Use of OC in past 3 months, or not had 2 normal menstrual periods since discontinuing OCs.				MAACL dysphoria scores	-5.71 vs -0.08 p=NS		Possible BDI scores range from 0 to 63, with 0-9 being the minimal or normal range, 10-16 mild depression, 17-29 moderate depression, 30-63 severe depression. MAACL-R consists of 132 adjectives describing mood.
								MAACL positive affect scores	-2.12 vs +0.08 p=NS		Scores from the test are converted into 5 subscales; anxiety, depression, hostility (which form the 'negative affect' or dysphoria scale), and sensation seeking and positive affect (which constitute the 'positive affect' scale). 30 (48%) returned for all visits. Baseline BDI scores significantly different between groups (10.8 DMPA vs 6.3 control, p<0.03)

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Westhoff 1998 [289] USA	Cross-sectional	3	495	At least 15 years of age, selecting a new contraceptive method, and had received contraceptive counselling in the clinic in the past 3 months.	DMPA (n=495)	-	1 year	Changes in depression scores in continuers vs discontinuers of DMPA use	At 1 year 44% continued, 56% discontinued. Baseline and 1-year scores in continuers: 7.4 and 6.7; and in discontinuers 8.0 and 8.0. (p=0.09 for difference in baseline scores)	(Partly) by the Kaiser Family Foundation and National Institute of Child Health and Human Development	DMPA users interviewed at 0 and 12 months. 393 (79%) completed follow-up interviews at 12 months. Depression scores derived by taking the sum of responses to 6 questions from the Mental Health Inventory. Possible range of scores was 0 to 24.

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Chapter 7 – Progestogen only injectable contraceptives: cardiovascular risks

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Enk 1990 [292] Sweden	Cohort	2-	29	Healthy, normolipidaemic menstrualting womern seeking injectable contraceptives	DMPA	NET	1 year	Serum and lipoprotein lipids	DMPA: 15% decrease in HDL-lipids NET: 30% decrease in HDL	Schering Upjohn	
Poulter 1998[110] Multinational: Africa Asia Latin America	Case-control	2+	13694	Women aged 20 to 44 years (15 to 49 years 3 of 21 centres) admitted to hospital with one of three cardiovascular disorders (stroke, venous thromboembolism, or acute myocardial infarction).	Oral or injectable progesterone-only or injectable combined hormonal contraceptives (n=3697, 1% being POIC users)	Nonusers of steroid hormone contraceptives (n=9997)	7 year recruitment period	Cardiovascular disease (CVD) risk	OR 1.02 (95%CI 0.68 to 1.54)	National Institutes for Health, UNDP/UNFPA/WHO World Bank Special Programme of Research	Adjusted OR presented.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Women were excluded if they had a transient ischaemic attack, had died within 24 hours of admission, had a history of VTE, stroke, or acute MI.				Stroke Venous thromboembolism Acute myocardial infarction	OR 0.89 (95%CI 0.53 to 1.49) OR 2.19 (95%CI 0.66 to 7.26) OR 0.66 (95%CI 0.07 to 6.00)		

1 **Chapter 7 – Progestogen only injectable contraceptives: Bone mineral density**

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Curtis 2004[295]	Systematic review	2++	31 studies (24 studies included DMPA; n=1797 users, n=2789 controls)	Women of any age	Current or past users of progestogen only contraceptives	Nonusers of progestogen only contraceptives (4 studies had no comparison group; 15 were never/nonusers; 1 IUD users; 1 'women from other studies'; 2 OC users; 2 Norplant users	>1 year (13 studies, not stated in others)	Bone mineral density	Changes in DMPA-users vs control or baseline inconsistent across studies. Current DMPA users generally had lower BMD than nonusers (within 1 SD so not clinically significant). No significant differences identified between past and never DMPA users.	WHO	All studies included were cross-sectional or longitudinal. Sites of BMD measurement were lumbar spine, femoral sites, forearm, and whole body. One objective of the review was to assess BMD and fracture risk in women aged <18 years or >45 years

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Fracture risk	In non-Hispanic white women, relative risk of stress fracture in current DMPA users was RR 1.71 (95%CI 1.01 to 2.90), not significant when adjusted for bone density (RR not reported).		Study followed US army recruits through 8 weeks of basic training to identify stress fractures.
Ryan 2002 [322] UK	Cross sectional	3	147	Women aged 15-49 years offered DMPA as contraception	DMPA given every 11-12 weeks	-	2 years	Bone densitometry at lumbar spine (LS) and femoral neck (FN) (only in women with serum estradiol levels less than 52 pmol/l (n=27), or with menopausal symptoms despite a higher estradiol level (n=5)	LS mean T score -1.08 (95% CI -1.41 to -0.75), and Z score -0.84 (-1.17 to -0.52). FN mean T score -0.55 (95% CI -0.87 to -0.23), and Z score -0.32 (95% CI -0.63 to -0.02)	Not stated	UK study set in a poor urban general practice. (Not included in Curtis systematic review). 99 (67% discontinued, so estradiol levels were only measured in 48 women after 2 years). These 48 women were all Caucasian. Mean duration of use in the 32 women in whom bone densitometry was measured was 52 months (SD 22). Mean weight of the 32 women who underwent bone densitometry (DEXA) was 67 kg.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Petitti 2000 [296] Bangladesh, Brazil, China, Egypt, Mexico, Thailand	Cross sectional	3	2474	Women aged 30 to 34 years with at least 2 years lifetime use of OCs, DMPA, or levonorgestrel implants. Not breast-feeding or recently breast-feeding, not recently pregnant, and not had hysterectomy or oophorectomy.	Ever users of: COC (n=819) DMPA 150 mg every 3 months (n=350) Levonorgestrel implant (Norplant, n=610)	Never users of hormonal contraceptives (or lifetime exposure of less than 6 months to them) (n=695)	-	BMD at distal radius	Adjusted mean differences in BMD between never users and the other groups presented in graphs only (all adjusted mean differences within 1 SD of the young adult reference mean). BMD in DMPA users significantly lower than never users but no significant difference between never users and COC or levonorgestrel	Not stated	WHO study of hormonal contraception and bone health). BMD measured by single X-ray absorptiometry Of the comparison group 78% had never used any form of hormonal contraception. In the 22% who had, mean duration of contraceptive use was 3 months (SD 1.6), and the mean time since stopping was 78 months (SD 50).

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source Of funding	Additional comments
				Exclusions: current or past use of drugs affecting calcium metabolism (anticonvulsants, corticosteroids, thiazides, calcium, vitamin D, thyroid drugs), or having conditions affecting calcium metabolism (chronic liver or kidney disease, hypo- or hyperparathyroidism, diabetes mellitus, cancer, rickets, pituitary disease).				BMD at midshaft of ulna	Adjusted mean differences in BMD between never users and the other groups presented in graphs only (all adjusted mean differences within 1 SD of the young adult reference mean). No significant differences between groups identified.		Of COC users, 82% used formulations containing between 30 microgram and 50 microgram of oestrogen, 15% more than 50 microgram, and under 1% less than 30 microgram (unknown in 2%). Women who had used more than one hormonal method were assigned to the hormonal method most recently used for 2 or more years.
Perrotti 2001 [297] Brazil.	Cross sectional	3	189	Women aged 30 to 34 years who had used the contraceptive method for at least 2 years, and had never used another hormonal method. Not breast-feeding or recently breast-feeding, not recently pregnant, and not had hysterectomy or oophorectomy.	DMPA 150 mg every 90 days, (n=63)	Never users of hormonal contraceptives (n=63)	-	BMD at distal radius and midshaft of ulna (mean, g/cm^2)	Distal: 0.465±0.0.53 DMPA vs 0.469±0.042 COC vs 0.473±0.048 nonusers (p=NS between groups)	Not stated	Same inclusion criteria and endpoint as Petitti 2000[296]

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: current or past use of drugs affecting calcium metabolism (anticonvulsants, corticosteroids, thiazides, calcium, vitamin D, thyroid drugs), or having conditions affecting calcium metabolism (chronic liver or kidney disease, hypo- or hyperparathyroidism, diabetes mellitus, cancer, rickets, pituitary disease).	COC (ethinylestradiol 30 microgram, levonorgestrel 150 microgram), (n=63)			Ultradistal: 0.384±0.057 vs 0.393±0.042 vs 0.392±0.051 (p=NS between groups)		Mean duration of COC use was significantly greater than of DMPA use (68 months vs 42). BMD measured by single X-ray absorptiometry.
Bahamondes 1999 [298] Brazil	Cross sectional	3	100	Women aged 35 to 45 years who had used DMPA for at least 1 year, and had never used another hormonal method. Not breast-feeding in last 12 months.	DMPA 150 mg every 3 months for 1 year (n=50)	Women who had not used DMPA or other hormonal method for more than 5 months (n=50)	-	BMD at distal radius and midshaft of ulna	BMD in distal radius significantly lower in DMPA users vs never users. No significant difference between groups in BMD at the midshaft of the ulna.	Not stated (equipment for bone scanning donated by WHO).	BMD measured by single X-ray absorptiometry. Mean age of women was 39.8 ± 4.2 years in the DMPA group and 39.8 ± 4.4 years in the never user group. Mean duration of DMPA use was 46.4 ± 38.6 months.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: current or past use of drugs affecting calcium metabolism (anticonvulsants, corticosteroids, thiazides, calcium, vitamin D, thyroid drugs), or having conditions affecting calcium metabolism (chronic liver or kidney disease, hypo- or hyperparathyroidism, diabetes mellitus, cancer, rickets, pituitary disease).						

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Naessen 1995 [321] Sweden	Cohort	2-	19	Women seeking contraceptive advice at a hospital family planning unit and wiling to try DMPA or Norplant. Not used OC in the last 3 months, and without any diseases or medications known to interfere with bone density.	DMPA 150 mg by intramuscular injection every 12th week (n=10)	Norplant (releasing 30g to 60g levonorgestrel/day during the first year of use) (n=9)	6 months	Serum levels of markers of bone metabolism (calcium, alkaline-phosphatase, osteocalcin, oestradiol) Urinary calcium/ creatinine ratio, and hydroxylproline/ creatinine ratio	In the DMPA group serum calcium, osteocalcin, and urine hydroxyproline/ creatinine ratio increased. In the Norplant group, alkaline phosphatase, osteocalcin, and estradiol levels increased significantly.	Grants from Family planning fund Uppsala, Sweden, and Swedish Medical Research Council.	19 completed, forearm bone density measured in 18. BMD measured by single photon absorptiometry.
								BMD in distal and proximal forearm (change from baseline)	Fell in DMPA group (-0.41%, p=NS), and increased significantly in Norplant group (+2.94%). Between-group differences not significant.		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Orr-Walker 1998 [314] New Zealand	Survey	3	346 (of whom 34 reported past use of DMPA)	Post-menopausal women with no disorders of calcium metabolism, or renal, thyroid, or hepatic dysfunction. Not taking drugs known to affect calcium metabolism, or used hormone replacement therapy for more than 6 months.	Previous use of DMPA (n=34)	No previous use of DMPA (n=312)		BMD of whole body (g/cm^2)	1.060 ± 0.013 past DPMA use vs 1.056 ± 0.004 no past use. Between-group difference 0.004 (95% CI -0.023 to 0.031)	Health Research Council of NZ.	BMD measured using dual X-ray absorptiometry. 22 of the 34 past DMPA users were also past oral contraceptive users. Median age at which DMPA use began was 41 years (range 28 to 50), and median duration of use was 3 years (range 0.2 to 18.1). Mean age of women at the time of the survey was 60 ± 5 years
								Lumbar spine, (g/cm^2).	1.07 ± 0.03 vs 1.05 ± 0.01 Between-group difference 0.020 (95% CI -0.034 to 0.074)		
								Femoral neck (g/cm^2).	0.84 ± 0.02 vs 0.86 ± 0.01 Between-group difference -0.018 (95% CI -0.055 to 0.019)		
								Ward's triangle (g/cm^2).	0.67 ± 0.02 vs 0.71 ± 0.01 Between-group difference not reported		
								Trochanter (g/cm^2)	0.75 ± 0.01 vs 0.74 ± 0.02 Between-group difference -0.012 (95% CI -0.047 to 0.023)		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Taneepanichskul 1997 [302] Thailand	Survey	3	100	Women aged 24 to 48 years who had used DMPA for at least 36 months. IUD users selected as controls. No history of smoking alcohol intake, metabolic bone disease, or had conditions or took drugs known to affect bone and mineral metabolism.	DMPA (n=50)	IUD users (never used hormonal contraception) (n=50)	-	BMD at distal and ultradistal forearm	Distal: 0.48 ± 0.05 vs 0.48 in both groups (95% CI -0.02 to 0.02) Ultradistal: 0.38 ± 0.06 vs 0.4 ± 0.05 (95% CI -0.04 to 0.001).	Ramathibodi Research Foundation, Faculty of Medicine, Ramathibodi Hospital, Mahidol University	BMD measured using dual X-ray absorptiometry. Mean duration of DMPA use was 59.14 ± 30.73 months, and of IUD was 47.7 ± 31.31 months.
								Serum estradiol levels, mean (picogram/ml)	Significantly lower in DMPA group 52.67 ± 25.1 vs 147.51 ± 91.9 (95% CI -122 to -68.1)		
Lara-Torre 2004 [310] USA	Cohort	2-	148	Adolescents aged 11 to 21 years who were new users of DMPA or COC. Control group was those in the same clinic using barrier methods, or other adolescents in a paediatric and adolescent gynaecology private office..	DMPA (n=58)	COC (n=71) Control group (non users of contraception) (n=19)	2 years	Lumbar spine BMD at 6, 12, 18, and 24 months	Mean % changes in BMD at 6, 12, 18, 24 months were: -0.25%, -1.59%, -2.91%, -1.85% (DMPA); +1.17%, +2.35%, +3.82%, -1.01% (COC); +2.77%, +2.45%, +0.73%, +5.89% (control)	Alliant Community Trust Foundation	BMD measured using dual X-ray absorptiometry. The proportion of Caucasian girls was significantly less, and the African-American proportion significantly higher in the DMPA group vs control.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				Exclusions: pregnancy, or a medical condition that could affect BMD, growth, or mineralization.					Significantly reduced in DMPA group vs control at all time points, and compared with COC users at 12 and 18 months. No significant differences detected between COC users and nonusers		The attrition rate was 48% at 6 months, 64% at 12 months, 73% at 18 months, and 78% at 24 months. At 24 months, 21 DMPA users, 5 COC users, and 6 girls from the control group remained. Mean age of girls across the three groups was 14 to 15 years (range 11 to 21).
Cromer 1996 [317] USA	Cohort	2-	48	Postmenarchal adolescent girls (aged 12 to 21 years) who had not previously used hormonal contraception, and who chose DMPA, Norplant, or a COC. Exclusions: medical conditions or treatments with potential influences on skeletal growth or mineralization; confidentiality issues related to contraception.	DMPA (n=15) COC (n=9) Norplant (n=7)	Girls choosing barrier methods or who were abstaining from sexual intercourse (n=17).	1 year	Lumbar spine BMD	-1.53% DMPA vs +2.46% Norplant vs +1.52% COC vs +2.85% control at 1 year. In the 15 girls followed up for 2 years, changes in BMD were -3.12% DMPA vs +9.33% Norplant vs +9.49% control.	Not stated	The COC contained 30 micrograms of ethinylestradiol and 150 micrograms of desogestrel. Mean ages across groups was 14.2 to 15.5 years (girls in the control group were significantly older than the DMPA or COC groups). BMD measured using dual X-ray absorptiometry.

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									Changes in DMPA group significant compared with other groups at 1 and 2 years. BMD values not significantly different among groups at 1 year. Norplant users had significantly higher BMD than DMPA users or the control group at 2 years.		BMD measurements were repeated at 2 years in 15 girls (8 DMPA, 0 COC, 3 Norplant, 4 control). There were significantly more black girls in the DMPA group vs other groups. Norplant users reported significantly more aerobic exercise than other groups.
Scholes 2004 [308]	Cross sectional	3	174	Girls aged 14 to 18 years using DMPA. Exclusions: pregnancy, breast-feeding, cancer in past 10 years, other conditions known to affect bone density, taking steroids or other medications known to affect bone metabolism.	DMPA users, 150 mg every 3 months (n=81)	Nonpregnant women of similar age (n=93)	-	Whole body BMD (mean [SD], g/cm^2)	1.078 (0.011) DMPA users vs 1.086 (0.011), p=NS	Not stated	The results presented are baseline data from an ongoing longitudinal study of factors affecting BMD in adolescent women. BMD measured using dual X-ray absorptiometry. 17 (18%) of the comparison group were using a OC.
								Total hip BMD (mean [SD] g/cm^2)	0.940 (0.013) vs 0.970 (0.013), p=NS		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				(In the comparison group, other exclusions were past use of DMPA, and those who had not yet had their first period).				Lumbar spine BMD (mean [SD] g/cm^2)	0.970 (0.012) vs 0.992 (0.012), p=NS		Significantly more DMPA users were smokers (36% vs 11%, p<0.0001). Median duration of DMPA use was 9 months (range 1 to 39). 30% had received 1 injection, 32% 2-3, 21% 4-7, 17% 8 or more. BMD according to number of injections also presented.
Scholes 2002 [304] USA	Cross-sectional	3	457	Women aged 18 to 39 years who were new or prevalent DMPA users. Exclusions: pregnancy, breast-feeding, and conditions/drugs known to affect BMD	DMPA 150 mg every 3 months (n=183)	Women not exposed to DMPA (n=274, of whom ~34% were OC users)		Lumbar spine BMD (mean g/cm^2)	1.018 ± 0.009 DMPA users vs 1.044 ± 0.007, p=0.03	Not stated	The results presented are baseline data from a prospective cohort study.[306] BMD measured using dual X-ray absorptiometry.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
				(hysterectomy, oophorectomy, endometriosis, kidney/liver disease, metabolic bone disease, cancer in past 10 years; use of steroids, anticonvulsants, bisphosphonates)				Femoral neck BMD (mean g/cm^2)	0.838 ± 0.010 vs 0.857 ± 0.008, p=NS		Median duration of DMPA use was 11.3 months (range 1 to 133). 24% were new users.
								Trochanter BMD (mean g/cm^2)	0.696 ± 0.008 vs 0.724 ± 0.007, p<0.01		23% were seen within 1-3 months of use, 36% within 4-12 months, 22% within 13-24 months, 19% after 25 months of use or more.
								Total body BMD (mean g/cm^2)	1.085 ± 0.006 vs 1.091 ± 0.005, p=NS		In those aged 18 to 21 years (48 DMPA users vs 62 nonusers), BMD significantly lower in DMPA users at all sites measured p<0.01.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Scholes 2002 [306] USA	Cohort	2+	457	Women aged 18 to 39 years who were new or prevalent DMPA users. Exclusions: pregnancy, breast-feeding, and conditions/drugs known to affect BMD (hysterectomy, oophorectomy, endometriosis, kidney/liver disease, metabolic bone disease, cancer in past 10 years; use of steroids, anticonvulsants, bisphosphonates)	DMPA 150 mg every 3 months (n=183)	Women not exposed to DMPA (n=274, of whom ~34% were OC users)	3 years	Lumbar spine BMD (mean g/cm^2)	Change per 6-month interval -0.0053 (95% CI -0.0069 to -0.0037) in continuous DMPA users; +0.0067 (95% CI +0.0047 to +0.0088) in DMPA discontinuers; +0.0023 (95% CI +0.0014 to +0.0032) in nonusers. Annualized mean rate of change -0.87% in continuous DMPA users, +1.41% in DMPA discontinuers, +0.4% in nonusers.	Not stated	Longitudinal data from cross-sectional study.[304] BMD measured using dual X-ray absorptiometry. Median duration of DMPA use at baseline was 11.3 months (range 1 to 133). 24% were new users. % completing clinic visits were 87% at 1 year, 76% at 2 years, 67% at 3 years. Of the DMPA users, 60% discontinued this method during follow-up, (44% within the first 6 months); discontinuers were followed up for a mean of 15 months (range 6 to 30).

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Proximal femur BMD (mean g/cm^2)	Change per 6-month interval -0.0060 (95% CI -0.0075 to -0.0046) in continuous DMPA users; +0.0035 (95% CI +0.0019 to +0.0050) in DMPA discontinuers; -0.0002 (95% CI -0.0087 to +0.0082) in nonusers. Annualized mean rate of change -1.12% in continuous DMPA users, +1.03% in DMPA discontinuers, -0.05% in nonusers.		BMD in lumbar spine signficiantly lower in DMPA users at baseline.[304]

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Gbolade 1998 [300] UK	Cross sectional survey	3	181	DMPA users who had amenorrhoea for more than 1 year or had used the method for more than 5 years. Aged 17 to 52 years (mean 33).	DMPA users (n=181)	-	-	Lumbar spine BMD vs age-matched normal values (Z score)	-0.332 (95% CI -0.510 to -0.154) p<0.001 vs 'normal' population	None stated.	BMD measured using dual X-ray absorptiometry. Median duration of DMPA use was 5 years (range 1 to 16).
								Proximal femur BMD vs age-matched normal values (Z score)	-0.088 (95% CI -0.237 to +0.060) p=0.25 vs 'normal' population		
								Serum oestradiol levels	82% were <150 picamol/l, 18% were >150 picamol/l. Range of levels 37 to 318. BMD and oestradiol levels not found to be related.		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Berenson 2001 [318] US	Cohort	2+	346	Women aged 18 to 33 years who had undergone a bone scan as part of a large contraceptive study. All had met entry requirements to Armed Forces. Exclusions: pregnancy, breast-feeding, had used an injectable contraceptive in past 6 months or taken an oral contraceptive in the last month, or had contraindications to hormonal contraception.	DMPA 150 mg every 3 months (n=96) COC containing 35 microgram ethinylestradiol + 1 mg norethindrone (n=87) COC containing 30 microgram ethinylestradiol + 150 microgram desogestrel (n=92)	Women who chose not to use hormonal contraception (n=71)	1 year	Lumbar spine BMD	Mean changes: -2.74% (95% CI -4.44% to -1.05%) DMPA +2.33% (95% CI +0.53% to +4.12%) norethindrone COC +0.33% (95% CI -1.30% to +1.96%) desogestrel COC -0.37% (95% CI -1.98% to +1.25%) control DMPA vs control, and norethindrone COC vs control p=0.01. DMPA vs either COC p<0.002.	Department of Defence	Women allowed to choose between injectable and oral contraceptive; then oral contraceptive was allocated randomly by random numbers table. BMD measured using dual X-ray absorptiometry. 39% of hormonal method users discontinued during the 1 year study. Final analysis was only performed in 96 (35%) hormonal contraceptive users, and 59 (83%) of the control group. There were significantly fewer smokers in the oral contraceptive group vs DMPA or control.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Merki-Feld 2003 [307] Switzerland	Cohort	2+	45	Healthy premenopausal Caucasian women aged 30-45 years from a University hospital family planning centre. Exclusions: contraindications to DMPA, smoking more than 10 cigarettes per day, regular alcohol intake, congenital or acquired bone disease, family history of osteoporosis, BMI <17 kg/m^2, intense practice of physical exercise, pregnancy, breast-feeding, immobilisation in past 6 months, thyroid/parathyroid diseases, COPD, malabsorption, thalassaemia minor, drugs affecting bone and mineral metabolism	DMPA 150 mg by intramuscular injection every 12 weeks (n=35)	Users of nonhormonal contraceptive methods (n=10)	2 years (DMPA) 1 year (control)	Cortical bone mass in non-weight bearing radius	Changes in year 1, mean (SD) : -0.26% (0.6) DMPA, +0.09% (0.5) control, p<0.04 between groups	Pharmacia & Upjohn	DMPA users started the method at an age older than 23 years (mean 35.1). Women with trabecular bone loss of more than 1% after 1 year (n=6) , and 1 woman with osteopenia received calcium or oestrogen during the second year of follow up. 32 DMPA users and all of the control group completed 1 year of follow-up. 23 DMPA users completed 2 years follow-up. Peripheral quantitative computed tomography (pQCT) was used to measure bone density.
								Trabecular bone mass in non-weight bearing radius	Changes in year 1, mean (SD) : +0.08% (1.6) DMPA, +0.32% (1.1) control, p=NS between groups		

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Tharnprisarn 2002 [316] Thailand	Cross sectional	3	60	Women aged 15 to 30 years who had used the contraceptive method for at least 2 years. No smoking or alcohol intake, no diseases or medications that affect hormonal status or bone metabolism. Not pregnant or breast-feeding.	DMPA (n=30)	OC (n=30)	-	BMD at distal forearm (g/cm^2)	0.566±0.043 DMPA vs 0.571±0.064 OC (p=NS)	Not stated	BMD measured by dual X-ray absorptiometry. Mean duration of use of DMPA 27.8±14.6 months, and OC 24.1±14.0 months. Type of OC used not recorded.
								BMD at ultradistal forearm (g/cm^2)	0.403±0.039 DMPA vs 0.423±0.048 OC (p=NS)		
Wanichsetakul 2002 [315] Thailand.	Cross sectional	3	155	Women aged 30 to 34 years using COC or DMPA for at least 2 years. Exclusions: pregnancy or breastfeeding (current or past 6 months), current use or in last 3 months of drugs known to affect calcium metabolism, chronic diseases affecting bone metabolism, oophorectomy, ovarian dysfunction, BMI below 5th or above 95th percentile.	DMPA (n=34)	COC (n=59) Nonusers of hormonal contraceptives (n=62)	-	Lumbar spine BMD (mean, g/cm^2)	1.031±0.090 DMPA vs 1.065±0.121 COC vs 1.096±0.116 nonusers (DMPA vs nonusers p=0.007)	Not stated	BMD measured by dual X-ray absorptiometry. Mean duration of use of DMPA 55.76±35.31 months, and COC 57.36±27.02 months.
								Femoral neck BMD	0.915±0.090 vs 0.933±0.120 vs 0.894±0.109		
								Ward's triangle BMD	0.833±0.137 vs 0.849±0.152 vs 0.794±0.154		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Greater trochanter BMD Ultradistal radius BMD Distal ulna BMD	0.793±0.065 vs 0.790±0.105 vs 0.759±0.089 0.44±0.056 vs 0.44±0.067 vs 0.429±0.062 0.621±0.058 vs 0.616±0.084 vs 0.597±0.075		
Cundy 1998 [299] New Zealand	Cross sectional	3	463	Women who had used DMPA for at least 2 years. Control data for European women were from premenoupausal European women who were volunteers providing normative data for studies, and healthy women in late 40s referred for BMD measurements. Control data for Polynesian women were taken from a previously published study.	DMPA (n=163)	Non DMPA users (n=300)	-	Lumbar spine BMD	1.352 g/cm^2 DMPA vs 1.204 control, p<0.001. Mean Z score in DMPA users -0.65 (95% CI -0.80 to -0.49).	Not stated	Women recruited from family planning clinics and local general practitioners. 82% were of European origin, and 18% were Maori/Polynesian. Median age ~43 years (range 18 to 54). Median duration of DMPA use was 12 years (range 2 to 26), but was significantly longer in Polynesian women.

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
											Women starting DMPA before age 21 years, and those using the method for more than 15 years had lower Z scores than those starting DMPA after age 21, and using it for less than 15 years. BMD measured by dual X-ray absorptiometry.
Tang 1999 [301] China	Cross sectional	3	285	Women using DMPA for at least 5 years, recruited from the Hong Kong family planning association. Age-matched control group taken from a cross sectional study on BMD in Hong Kong	DMPA (n=67)	Nonusers of hormonal contraception (n=218)	-	Lumbar spine BMD (mean, g/cm^2)	0.93 DMPA vs 1.03 control, p=0.001	Not stated	BMD measured by dual X-ray absorptiometry. Mean age of DMPA group 42.8 years vs 40 control (range 34 to 46). Median duration of DMPA use 6 years (range 5 to 15).
								Femoral neck BMD	0.69 vs 0.83, p=0.001		
								Trochanter BMD	0.59 vs 0.71, p=0.001		
								Ward's triangle BMD	0.58 vs 0.78, p=0.001		

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Paiva 1998 [303] Brazil	Cross sectional	3	136	DMPA users of at least 1 year, aged 20 to 45 years. Control group regularly menstruating nonusers. Exclusions: women with history of metabolic bone disease or any other pathological condition, or taken drugs known to affect bone mass.	DMPA 150 mg every 12 weeks (n=72)	Non DMPA users (lifetime use of hormonal contraceptives under 2 years) (n=64)	-	Lumbar spine BMD (mean, g/cm^2)	1.12 DMPA vs 1.21 control, p<0.001	FAPESP (Fundacao de Amparo a Pesquisa do Estado de Sao Paulo	Mean duration of DMPA use was 42 ± 26.3 months. BMD measured by dual X-ray absorptiometry.
								Femoral neck BMD	0.98 vs 1.04, p=0.01		
								Trochanter BMD	0.78 vs 0.84, p<0.002		
								Ward's triangle BMD	0.90 vs 0.97, p=0.005		

A T score is the number of standard deviations by which the individual's BMD differs from the mean peak BMD for young adults of the same gender. For every standard deviation below the mean, the risk of fracture is approximately doubled. A T score of between -1 and -2.5 indicates osteopenia, and of -2.5 or less indicates osteoporosis.
A Z score is the number of SDs by which the individual's BMD differs from the mean BMD for people of the same age.

Chapter 7 – Progestogen only injectable contraceptives: Management of oestrogen deficiency induced by DMPA

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Cundy 2003 [323]	RCT	1+	38	Lon-term DMPA users (mean age 37)	Oestrogen replacement therapy (n=19)	Placebo (n=29)	2 year	Spinal BMD	At 2 years Oestrogen group: Mean increase of 1% Placebo: Drop of 2.6% Between group differences: 2.0% at 12 months (p<0.058) 3.2% at 18 months (p<0.01) 3.5% at 24 months (p<0.002)	Not stated	

Chapter 7 – Progestogen only injectable contraceptives: follow-up reminder

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Keder 1998 [349] USA	RCT	1+	250	Women attending a hospital clinic, not currently receiving DMPA, and not immediately postpartum.	DMPA with appointment reminder (written reminder sent 2 weeks prior to next injection, plus a telephone call if did not attend their appointment)	DMPA with no appointment reminder	1 year	Missed appointments	39% vs 33%, relative risk 1.16, 95%CI 0.83 to 1.62	Not stated	Missed appointment results are given for those not known to have discontinued DMPA intentionally.
								Continuation rates	43% vs 45%, relative risk 0.94, 95%CI 0.71 to 1.25		

Chapter 7 – Progestogen only injectable contraceptives: Breastfeeding

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Halderman 2002[341] USA	Cohort	2+	319	Postpartum women who intended to breastfeed	Progestogen-only contraception users (n=181, of whom 102 used DMPA, 77 a POP, and 2 a levonorgestrel implant)	Nonhormonal contraception users	6 weeks postpartum	Breast-feeding continuation rate	74.1% DMPA vs 72.1% hormonal users vs 77.6% nonhormonal users	National Institutes of Health	DMPA administered a mean of 51.9 hours after delivery (range 6.25 to 132 hours). DMPA users were younger than users of nonhormonal contraception (mean 25.7 vs 29.4 years), had lower gravidity and parity, and less experience with prior breast-feeding (46% vs 62%).
								Breast-feeding status	Exclusively; 36.5% vs 36% vs 34.8% With bottle supplementation; 63.5% vs 64% vs 65.2% Not breast-feeding (bottle only) due to insufficient milk 27.3% vs 34.9% vs 50%		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Hannon 1997 [342] USA	Cohort	2+	103	Women who had delivered a healthy neonate, were breast-feeding at the time of hospital discharge and intended to continue, and chose DMPA or nonhormonal contraception. Women choosing to use a IUD, levonorgestrel implant, or OC within 4 weeks postpartum were excluded	DMPA (n=43)	Nonhormonal contraception users (n=52)	16 weeks postpartum	Breast-feeding continuation rate	37% vs 27%	National Institutes for Health, and The Thomas Wilson Sanitarium for Children of Baltimore City	Follow-up completed for 90 women. DMPA users were younger than users of nonhormonal contraception (mean 23 vs 25 years), and fewer were married (12% vs 29%).
								Duration of breast-feeding (median)	10.14 weeks (95% CI 0.71 to 19.57) vs 6.57 (95% CI 3.43 to 9.71)		
								First introduction of formula feed (median)	15 vs 14 days		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Baheiraei 2001 [340] Iran	Cohort	2-	140	Women who were exclusively breast-feeding, and 6 weeks postpartum	Progestogen-only contraception (n=51)	Non-hormonal contraception (n=89)	Infant's 26th week	Milk composition	Mean milk concentrations of calcium, phosphorus, sodium, potassium, and protein similar in both groups. Triglyceride levels significantly higher in the progestogen-only group. Magnesium levels significantly higher in the non-hormonal group.	Not stated	
								Infant growth	Body weight and length similar in both groups. Head circumference higher in the progestogen-only group at 10-13 weeks.		

Chapter 8 Progestogen only subdermal implants: pregnancy rates, discontinuation rates, adverse effects, return of fertility after removal

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Newton 2003 [354] **Multicentred:** **Thailand** **Indonesia** **Europe** **Chile/Hungary** **Canada** **Finland** **Sweden** **Singapore** **UK** **USA** **China** **Associated references:** [54;351;355-364;400;403;484;485]	**Meta-analysis**	**1- - 2-**	**8 RCTs** **12 cohort studies**	**Women aged 18-40 years; sexually active and of childbearing potential; regular menses and in good health**	**Implanon (n=2423; 75,050 cycles)**	**Norplant (n=819; 28,109 cycles)**	**1-5 years**	**Pregnancy rates/100 woman years**	**0 in both groups**	**Organon** **Data provided by Organon**	**Trials performed during clinical development of Implanon: multicentre and single centre trials in Europe, SE Asia and North and South Americas.** Information received in July 2004 from **Organon** that, as a result of protocol violation, data from 5 trials (3 RCTs, 2 case series) carried out in Indonesia were to be excluded. Revised analysis including data from new trials will be available in September/October 2004. No further information has been received since. Data to be interpreted with caution

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Ectopic pregnancy	**None in either group**		
								Menstrual disturbances at 2 years	**Amenorrhoea: 21.7% vs 4.7%** **Infrequent bleeding: 27.3% vs 21.1%** **Frequent bleeding: 6.1% vs 3.4%** **Prolonged bleeding: 12.1% vs 9.0%**		
								Dysmenorrhoea	**Implanon** **Improvement: 35%** **Exacerbation: 3.4%** **Norplant:** **Overall improvement to a lesser extent (no data)**		
								Weight changes	**Increase of > 10% from baseline: 8.7% in both groups**		
								Mood changes/libido	**Emotional lability: 4.9% vs 7.6%** **Decreased libido: 3.3% vs 5.4%**		
								Skin effects	**Acne: 18.5% vs 21.2%**		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Blood pressure **Headaches** **Discontinuation rates (due to adverse events)** **Complication at insertion** **At removal** **Return of fertility**	**Systolic blood pressure of > 140 mmHg** **Diastolic blood pressure of > 90 mmHg** **0.8% in both groups** **16.8% vs 20.1%** **6% vs 7.9%** **0.3% vs 0%** **0.2% vs 4.8%** **Pain:** **0.9 % vs 1.9%** **Ovulation at 3 months:** **93.6% vs 90.9%**		
PMSN 2001 [174] [369] **Multicentre:** **Chile** **Columbia** **Egypt** **Sri Lanka** **Thailand** **Indonesia** **Bangladesh** **China**	**Cohort Multicentre study**	**2+**	**16,021**	**Women aged 18-40 years attending family planning clinics who wanted to use Norplant**	**Norplant (n= 7977)**	**Controls: IUD (n=6625) Tubal sterilisation (n=1419)**	**5 years**	**Cumulative pregnancy rates/100 woman years**	**Significant differences:** **At 1 year** **Norplant: 0.12** **Copper IUD: 1.02** **Non-copper IUD: 6.34** **Sterilisation: 0.21** **At 3 years** **Norplant: 0.53** **Copper IUD: 3.04**	**Family Health International, Population Council, Rockefeller Foundation**	**5 year follow-up completed by 94.6% of women** **IUDs may include non-copper IUDs unless stated** **Population difference: developing countries**

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
									Non-copper IUD: 11.68 Sterilisation: 0.5 At 5 years Norplant: 1.46 Copper IUD: 4.19 Non-copper IUD: 13.00 Sterilisation: 0.72		
								Cumulative discontinuation rate/100 woman-years	Significant differences: At 1 year Norplant: 4.6% Copper IUD:7.2% At 3 years Norplant: 20.9% Copper IUD:21.2% At 5 years Norplant: 33.2% Copper IUD: 30.5%		
								Discontinuation rates due to bleeding problems	Significant differences: At 5 years Norplant: 13.7% Copper IUD: 6.4%		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Weight change	**Significant differences: Weight gain: Norplant: 4.5% IUD; 0.9% Sterilisation:0 Adjusted RR 6.94 (95% CI 4.57 to 10.5) Weight loss: Norplant:1.2% IUD: 0.5% Sterilisation: 0.1% Adjusted RR 2.64 (95%CI 1.49 to 4.67)**		
								Bleeding disturbances	**Requiring hospitalisation: No significant differences Norplant: 0.2% controls 0.2% Adjusted RR 1.36 (95% CI 0.49 to 3.75)**		
								Anaemia	**No significant difference; Norplant:1.5% Controls: 1.9% Adjusted RR 0.80(95% CI 0.56 to 1.16)**		
								Amenorrhoea	**Significant differences: Norplant: 15.5% Controls: 3.3% Adjusted RR 5.08 (95% CI 4.16 to 6.20)**		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Mood disorders	**Significant differences: Norplant: 2.8% IUD: 1.2% Sterilisation: 2.2% RR 2.15 (95% CI 1.53 to 3.02)**		
								Premenstrual tension	**Significant differences: Norplant: 1.3% IUD: 0.7% Sterilisation: 0.8% RR 2.00 (95% CI 1.23 to 3.25)**		
								Acne	**Significant differences: Norplant: 0.9% IUD: 0.2% Sterilisation: 0 Adjusted RR 7.48 (95% CI 2.90 to 19.3)**		
								Headaches migraine	**Significant differences: Norplant: 11.5% IUD: 2.1% Sterilisation: 10.6% RR 3.44 (95% CI 2.83 to 4.18)**		
								Hypertension rate	**No significant differences: Norplant: 0.7 IUD: 0.4 Sterilisation: 0.4 Adjusted RR 1.78 (95% CI 0.93 to 3.40)**		

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Abdominal pain	**Significant differences: Norplant: 0.5% IUD: 1.1% Sterilisation: 2.6% RR 0.37 (95% CI 0.21 to 0.65)**		
								Recovery of fertility	**Significant difference: Conception within 1 year: Norplant: 55.6% IUD: 63.9%**		
Kurunmaki 1983 [370] **Finland**	Cohort	2+	**59**	**Healthy volunteers following legal termination of pregnancy**	**Norplant**	**Nova T (?? 380)**	**1 year**	**Pregnancy rates**	**None in both groups**	**Population Council Rockefeller Foundation**	**Use Norplant data only**
								Discontinuation rate	**At 1 year Norplant: 8.3% Nova T: 26.1%**		
								Reasons for removal	**At 1 year Bleeding/spotting: Norplant: 5.5% Nova T: 17.4% Amenorrhoea: Norplant: 2.8% Nova T: 0%**		
								Menstrual disturbances	**Significant Increase: Dysmenorrhoea: Norplant: 6% Nova T: 33% Menstrual flow: Norplant: 14% Nova T: 43%**		**Use Norplant data only**

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Weight change	No significant change from baseline in both groups		
Cromer 1996 [317] USA	Cohort study	2-	48	Adolescents age 12 to 21	Norplant (n=7)	DMPA (n=15) OC (n=9) Controls (No hormonal treatment)(n=17)	2 years	Menstrual disturbances Appointment compliance rate	At 6 months Amenoorhoea: Norplant: 36% DMPA: 60% COC: 8% Irregular bleeding: Norplant: >80% DMPA: >80% Maintained regular bleeding: COC: 80% At 6 months: Norplant: 40% DMPA: 78% COC: 46%	Roessler Foundation U of Ohio	Small sample
Darney 1999 [55] USA	Cohort	2+	399	adolescent teenagers	Norplant	COC condoms	2 year	Pregnancy rate Cumulative discontinuation rates	Norplant users: None COC users: 30% Condom users: 33% at 2 years At 1 year Norplant users: 18% COC users: 60% Condom users 48% At 2 years Norplant users: 36% COC users: 64% Condom users: 58%	Henry J Kaiser Foundation, USA	Loss to follow-up: 13% at 1 year (347 remaining) 14% at 2 years (345 remaining)

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Smith 2002 [486] UK	Retrospective review and postal survey	3	190	Implanon users in 2 clinics (women aged 13 – 51)	Implanon	None	6-12 months	Pregnancy rates Discontinuation rates Reasons for discontinuation	None 16% at 6 months 33% at 12 months Bleeding problems: 34% Mood swing: 24% Headaches: 17% Weight gain: 12%	Community Health Care Service, North Derbyshire	44% responded to postal survey
Fleming 1998 [373] UK	Cohort study	2+	755	Norplant users (mean age 27 years) and non-hormonal IUD users (mean age 31 years)	Norplant	Non-hormonal IUD	2 yrs	Discontinuation rates	Significant differences: At 1 year Norplant users: 16% IUD users: 30% At 18 months Norplant users: 20% IUD users: 37% At 2 years Norplant users: 28% IUD users: 43%	Not stated	

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Reasons for discontinuation	**Bleeding problems:** **Norplant: 45%** **IUD: 38%** **Menorrhagia: associated pain:** **Norplant: 4%** **IUD: 15%** **Mood swings:** **Norplant: 39%** **IUD: 0%** **Weight gain:** **Norplant: 16%** **IUD: 0%** **Headache:** **Norplant: 13%** **IUD: 0%** **Acne:** **Norplant: 7%** **IUD: 0%**		

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Chapter 8 Progestogen only subdermal implants: effects on cardiovascular parameters

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Egberg 1998 [388] Sweden	RCT	1+	86	Implant users aged 18 to 40 years	Implanon	Norplant	6 months	Haemostasis	Coagulation times: very small change from baseline in both groups	Organon	
Mascarenhas 1998 [389] UK	RCT	1+	60	Implant users aged 18 to 40 years	Implanon	Norplant	2 years	Apolipoprotein concentrations: A-I, A-II and B	No significant differences between the 2 groups	Organon	
Suherman 1999 [390] Jakarta	RCT	1-	90 45	Implant users aged 22 to 41 years Non-randomised Cu IUD 250 as control	Implanon	Norplant	3 years	Lipid metabolism: Cholesterol Triglycerides HDL LDL Apolipoproteins At 3-month intervals	Very small changes: No significant differences between the 2 groups Similar changes seen in IUD group	Organon	
Biswas 2003 [391] Singapore	RCT	1+	80	Implant users	Implanon (n=40)	Norplant (n=40)	2 years	Cholesterol Triglycerides HDL LDL	No significant changes and differences between the 2 groups	Not stated	
Biswas 2001 [393] Singapore	RCT	1+	80	Implant users	Implanon (n=40)	Norplant (n=40)	2 years	Carbohydrate metabolism: Oral glucose tolerance test at 6,12 and 24 months	Mild insulin resistance in both groups, no significant change in glucose levels in both groups	Organon	Lost to follow-up: 12 women

Chapter 8 Progestogen only subdermal implants: Bone mineral density

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Beerthuizen 2000 [396] Finland	Cohort study	2-	76	Women aged 18-40 years	Implanon (n=46)	Non-hormonal IUD (n=30)	2 years	Bone mineral density of lumbar spine, Proximal femur, Distal radius	Changes from baseline in BMD similar in both groups Clinical significant magnitude of 1 standard deviation not reached	Organon	Intention-to-treat: 73 women Both groups comparable in age, weight and body mass index, BMD and 17B-estradiol status
Banks 2001 [305] included studies from Sweden China USA Chile	Systematic review	2- to 3	1 RCT 3 cohort studies 2 non-comparative studies		Norplant	Non-users		Bone mineral density	Inconsistent and conflicting results One large cohort study [296] included in the review reported a decreased BMD among Norplant users	MRC, WHO	Studies reviewed were of poor quality

Chapter 8 Progestogen only subdermal implants: Specific groups of users

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Newton 2003 [354]	Meta-analysis	2-3	8 RCTs 12 cohort studies	Implanon users < 50 kg and > 70 kg	Implanon		1-5 years	Pregnancy rates	Women < 50 kg (n= 1235 women years): 0 at 3 years Women > 70 kg: at 1 year (n=161): 0 at 2 years (n=125): 0 at 3 years (n=78): 0	Organon	
Sivin 2000 [487] USA Dominican Republic	Analysis of a non-comparative study and a RCT	3	1210	Norplant users < 50 kg and > 80 kg	Norplant		7 years	Cumulative pregnancy rates	No significant differences: At 5 years: Women < 50 kg: 0 50-59 kg: 0.3/100 60-69 kg: 0.6/100 70-79 kg: 2.9/100 ≥ 80Kg: 8.1/100 Significant differences: at 7 years: Women < 50 kg: 0 50-59 kg: 1.0/100 60-69 kg: 0.6/100 70-79 kg: 4.8/100 ≥ 80Kg: 13.2/100		Unclear combination of data from 2 studies

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Cullins 1994 [406] USA	Cohort study	2+	678	136 adolescents (age 13-18) 542 adults (age 19-46)	Norplant		18 months	Pregnancy rate (method failure) Discontinuation rates Visit to clinic due to concern about irregular bleeding Removal of Norplant due to irregular bleeding	None in either groups At 1 year: Adolescents: 8% Adults: 10% At 18 months: 11% in both groups No significant difference: Adolescents: 57% Adults: 38% Adolescents: 6% Adults: 3%		
Levine 1996 [407] USA	Cohort study	2+	1688	674 adolescents (age 11-18) 1014 adults (age 19-49)	Norplant		50months	Pregnancy rates Discontinuation rates Reasons for implant removal	2 pregnancies (unclear which group) No significant difference: At 50 months: Adolescents: 6% Adults: 9% No significant difference: For both groups: Irregular menses: 28% Headaches: 20% Local arm irritation/pain: 16%	University funding	

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Berenson 1997 [408] USA	Case-control study	2-	112	Adolescents age 11 to 18	56 Norplant users	56 OC users	2 years	Pregnancy rate Discontinuation rate Adverse effects	Significant difference: At 1 year: Norplant users;0% OC users:25% Significant difference: At 1 year: Norplant users: 9% OC users: 66% Significant difference: Norplant users: 73% OC users: 5% No significant differences: Weight gain: 60% vs 53% headaches: 26% vs 42% Emotional problems: 26% vs 5% amenorrhoea: 6% vs 0% (Both groups gained weight at 12 months: 4 kg vs 2 kg)	Not stated	
Harel 1996 [278] USA	Cohort study	2-	66	adolescent s age 13 to 21	35 ex-DMPA users	31 ex-Norplant users	1 year	Reasons for discontinuation	Irregular bleeding: 60% vs 68% Weight gain: 40% vs 42% Increased headaches: 26% vs 35% Mood changes: 20% vs 42% Fatigue: 20% vs 29% Amenorrhoea: 14% vs 16% Loss of hair: 20% vs 10%	Maternal & Childhealth Grant	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
								Reestablishment of regular menstrual bleeding during the 1st month Cumulative pregnancy rate at 12 months	Significant differences: Ex-DMPA users: 50% Ex-Norplant users: 81% Significant differences: Ex-DMPA users: 20% Ex-Norplant users: 48%		
Dinerman 1995 [409] USA	Cohort study	2-	166	Women age 12 to 18	Norplant (n=54)	OC (n=64) Other methods (condoms or no method) (n=48)	6 months	Pregnancy rate Continuation rate Mean satisfaction score (Likert scale of 1-7) Report of adverse effects	Significant differences: Norplant: 2% OC: 20% Other methods:17% Significant differences: Norplant: 87% OC: 50% Similar in both groups Norplant: 5.4 OC: 5.6 Significant differences: Irregular menses: Norplant:89% OC: 59% Other methods: 54% Headaches: 39% vs 37% vs 10% Mood swings: 54% vs 32% vs 25% acne: 30% vs 12% vs 10% hair loss: 15% vs 0% vs 0% weight gain: 52% vs 40% vs 42%	NIH	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Polaneczky 1994[410] USA	Cohort study	2-	100	Post-partum adolescents	Norplant (n=48)	OC (n=50)	10months	Discontinuation rates Reasons for choosing Satisfaction with methods	Significant differences: Norplant: 5% OC: 67% Norplant: Difficulty in remembering pills: 71% Side-effects of OC: 38% Fear of pregnancy: 57% Ease of use: 48% Encouragement fro others: 34% Significant differences: Very satisfied: Norplant: 74% OC: 38% 'Would recommend to friends': Norplant: 95% OC: 79%	Research Foundation, U of Pennsylvania	Response rates: 86%
Cromer 1996 [317] USA	Cohort study	2-	48	Adolescents age 12 to 21	Norplant (n=7)	DMPA (n=15) OC (n=9) Controls (No hormonal treatment)(n=17)	2 years	Bone Mineral density (BMD)	No significant differences at 1 year: Norplant: increase of 2.46% DMPA: decrease of 1.53% OC: increase of 1.52% Controls: increase of 2.85% Significant differences: at 2 years: Norplant: increased total of 9.33% DMPA: decreased total of 3.12% Controls: increased total of 9.49%	Roessler Foundation U of Ohio	Small sample

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Dabrow 1995 [411] USA	Survey	3	112	adolescents age 13 to 20, including mothers	Norplant			Interest in Norplant Appealing features of Norplant Adverse effects	72% 'No daily pills': 87% effective: 81% Last for 5 years: 76% 'Don't need to do anything before sex': 76% Pimples: 87% Headaches: 83% Weight changes: 71% Menstrual changes: 71%	U of Michigan	
Reinprayoon 2000 [412] Thailand	Cohort study	2-	80	Mothers 6-weeks post-partum, age 18 to 40	Implanon (n=42)	Non-hormonal IUD (n=38)	4 months	Composition of milk	No significant differences in total fat, protein, lactose between both groups at 6 months	Organon	
Diaz 1999 [413] Chile	Cohort study	2-	108	Breastfeeding mothers 60 days post-partum, age 18 to 35	Norplant (n=29)	Cu IUD 380 (n=51) Progestogen vaginal ring (n=28)	2 years	Bone turnover and density at lumbar spine, serum calcium Phosphorus Alkaline phosphatases, parathyroid hormone FSH Lactation performance	No significant differences between groups at 1, 6 and 12 months Bone turnover higher at 1, 6 and 12 months after weaning: no difference among groups No significant differences between groups	Population Council	

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Mohllajee 2004 [338] included studies from Turkey	Systematic review	2- to 3	2 cohort studies 1 non-comparative study	231 women post-abortion	Norplant after 1st trimester abortion	IUD Withdrawal method		Menstrual disturbances Pregnancy rate	Inconsistent results (2 studies) None (1 study with no control group)	Studies funded by Population Council and Rockefeller Foundation	Studies reviewed were of poor quality Small sample
Gaffield 2004 [416] included studies from Finland, Sweden USA	Systematic review	2-	1 cohort study, 2 case reports	11 women with epilepsy	Norplant			Pregnancy rate and side-effects	Insufficient evidence Lower serum LNG levels in patients using phenytoin and carbamazepine No apparent harmful effect on seizure frequency	Most funded by drug companies	Studies reviewed were of poor quality
Diab 2000 [229] Egypt	Cohort study	2+	80	Women with controlled diabetes, age 20 to 40	Norplant (n=20)	DMPA (n=20) IUD (n=20) OC (n=20)	9 months	Glycaemic control Lipoprotein metabolism Coagulation profile	Minimal metabolic alterations in Norplant users Impaired glycaemic control and lipid profile in DMPA users	Not stated	
Taneepanichskul 2001 [488] Thailand	Non-comparative study	3	100	Women aged > 35 years	Norplant		1 yr	Pregnancy rate Side effects Blood pressure	None Amenorrhoea: 38% Irregular bleeding: 37% No significant difference	Not stated	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Curtis 2002 [230] studies from Thailand	Systematic review	3	2 non-comparative studies	Asymptomatic HIV+ve women (n=129)	Norplant			Blood pressure Body weight Haemoglobin level Side effects	No change at 12 months Bleeding, headaches, hair loss, acne: Same as uninfected women		

Chapter 8 Progestogen only subdermal implants: Insertion post-partum

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Phemister 1995 [402] USA	RCT	1+	250	Post-partum women	Norplant insertion 1-3 days post-partum (n=121)	Norplant insertion 4-6 weeks post-partum (n=120)		Tolerance Safety post-partum	No significant differences: Maternal weight Blood pressure Haemoglobin Significant differences: Duration of spotting and bleeding: 28.2 days ± 7.7 vs 22.4 days ± 7.3	Not stated	

Chapter 8 Progestogen only subdermal implants: Management of irregular bleeding

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]
Cheng 2000 [386] China	RCT	1-	100	Sino-implant users aged 18 to 40	Mifespristone 50mg (n=50)	Placebo (n=50)	1 yr	Bleeding patterns	Significant differences: Mean days of bleeding in 1st 90 days: Mifespristone: 48 ± 15 days Controls: 51± 15 days Average duration of bleeding episodes before and after treatment: Mifespristone: 14 days to 6.5 days Control: 15 days to 11 days	Not stated	Sino-implant: 2 rods each with 75mg LNG
Kaewrudee 1999 [380] Thailand	RCT	1+	67	Norplant users with irregular bleeding	Mefenamic acid 500 mg x 5 days (n=34)	Placebo (n=33)	4 weeks	Bleeding patterns	Significant differences: Bleeding stopped within 1 week after treatment: Mefenamic: 76% Placebo:27% Bleeding stopped within 4 weeks after treatment: Mefenamic: 68% Placebo:33%	University funding	2 patients dropped out from placebo group

									Mean no of bleeding days: **Mefenamic: 11.6 ± 8.2** **Placebo:17.2 ± 10.2**		

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Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Alvarez-Sanchez 1996 [381] Dominican Republic	RCT	1+	150	Norplant users with prolonged bleeding	COC (LNG-ethinyl estradiol) (n=45)	ethinyl estradiol 50 ug (n=43); Placebo (n=46)	20 days	Bleeding patterns	Significant differences: Bleeding stopped within 3 days: COC: 91% Ethinyl estradiol: 67% Placebo: 15% Bleeding stopped ≥ 7 days: 2% vs 14% vs 50% Mean no of bleeding days: 2.6 ± 1.4 vs 5.4 ± 5.1 vs 12.3 ± 5.4	Not stated	
Witjaksono 1996 [382] Indonesia	RCT	1-	48	Norplant users	Ethinyl estradiol 50 ug (EE)(n=18)	COC (LNG-ethinyl estradiol) (n=16) Placebo (n=14)	90 days	Bleeding patterns	Significant differences: Mean no of bleeding days: EE: 19.2 ± 3.4 COC: 18.2 ± 1.9 Placebo: 28.6 ± 5.4	WHO	Preliminary results
Massai 2004 [387] Chile	RCT	1+	120	Norplant users	Mifepristone 100 mg x 2 days at monthly intervals x 6 months (n=58)	Placebo (n=57)	13 months	Bleeding patterns	Significant differences: During treatment: Prolonged bleeding episodes: Mifepristone: 11 ± 3 days Placebo: 22 ± 23 days Total no of bleeding days: 1872 days vs 2855 days (35% lower in Mifepristone group) After treatment: No significant differences in both groups	WHO	

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding	Additional comments
Subakir 2000 [384] Indonesia	RCT	1-	72	Norplant users with bleeding problems	Vit E 200 mg daily (n=38)	Placebo (n=34)	30 days	Bleeding patterns	Significant differences: Number of bleeding days: Vit E:7.7 ± 1.4 days Placebo: 12.1 ± 1.3 days	WHO	Preliminary results
Boonkasemsanti 1996 [489] Thailand	RCT	1-	64	Norplant users with bleeding problems	Estradiol patch (n=33)	Placebo patch (n=31)	6 weeks	Bleeding patterns	No significant difference: 'Clinical improvement': Estradiol patch: 70% Placebo patch: 42%	WHO	
D'Arcangues 2004 [385] Multicentred: China Indonesia Chile Dominican Republic Tunisia	RCT	1+	486	Norplant users with bleeding problems	Vit E (n=120)	Aspirin (n=122) Vit E + Aspirin (n=121) Placebo (n=123)	1 year	Bleeding patterns	No significant differences in bleeding/spotting episodes, duration and length of bleeding-free intervals between the 4 groups	WHO	Intention-to-treat analysis

Chapter 9 Economic evaluation

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Sonnenberg et al, 2004 USA [417]	A cohort of sexually active women aged 15 to 50 years, who did not intend to become pregnant during the time horizon of the analysis, in a long-term mutually monogamous relationship and in average health (i.e. not in higher than average risk of breast cancer, or history of cardiovascular or thromboembolic disease). A Markov model was used to estimate costs and benefits per woman, resulting from each contraceptive method; the model included events such as contraceptive failure (leading to abortion, live birth, miscarriage, death due to delivery, ectopic pregnancy,), and adverse effects such as infections, cancer and cardiovascular events. Women that discontinued after contraceptive failure or adverse effects switched to another/no method, according to observed frequencies of use for women of the corresponding age. The time horizon of the model was 2 years.	Contraception; OC, patch, vaginal ring, IUD, IUS, diaphragm, condom, DMPA, monthly injectable, periodic abstinence, withdrawal, vasectomy, tubal sterilization. All methods were compared to "no method".	Total costs per patient over 2 years of use (including method costs, failure costs, costs of treating adverse effects): Vasectomy $902, DMPA $1022, IUD $1072, IUS $1075, patch $1742, vaginal ring $1842, condom $1939, OC $2011, monthly injectable $2067, periodic abstinence $2190, withdrawal $2597, diaphragm $4162, tubal sterilization $4931, no method $10,838. Number of pregnancies averted per woman compared to no method, over 2 years of use: vasectomy 1.47, DMPA 1.46, IUD 1.45, IUS 1.46, patch 1.39, vaginal ring 1.40, condom 1.25, OC 1.36, monthly injectable 1.46, periodic abstinence 1.19, withdrawal 1.14, diaphragm 0.98, tubal sterilization 1.46. Total QALYs per woman over 2 years of use: vasectomy 1.923, DMPA 1.930, IUD 1.921, IUS 1.929, patch 1.924, vaginal ring 1.924, condom 1.903, OC 1.921, monthly injectable 1.929, periodic abstinence 1.898, withdrawal 1.892, diaphragm 1.870, tubal sterilization 1.922, no method 1.783.	All methods were dominated by vasectomy; the only exception was DMPA, which showed an ICER of $18,064 per QALY compared to vasectomy.	• Model • US context, 2002 prices. • Comparisons of every method to "no method". • Birth costs include costs of newborns (normal or premature). • Time horizon was 2 years. • Side effects taken into account both as cost-incurring events and affecting utility. • Discontinuations considered only after failure or adverse effects (possibly underestimated). • Costs and benefits discounted at 3%. • 63.4% of pregnancies were considered mistimed; costs of pregnancy and delivery were discounted by 63.4% for analyses in which the time horizon exceeded 2 years. • Pregnancy outcomes and contraceptive effectiveness based on ranges of age. • Sensitivity analysis confirmed the robustness of the results. • Efficacy data for older methods reflect typical use; for newer methods data were imprecise. • Utility values based on the research team.	Cost-utility analysis and cost-effectiveness analysis	

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Study	Population Study method	Intervention Details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Trussell et al, 1997 USA [418]	A cohort of sexually active women aged 15-19. A model was used to project the 5 year costs by each contraceptive method, including method costs, failure costs, costs of side effects, and costs of treating STDs.	Contraceptive methods appropriate for adolescents: OC, implant, injectable, diaphragm, male condom, female condom, sponge, spermicides, cervical cap, withdrawal, periodic absistence.	Total costs (method + treatment of side effects + treatment of STDs + failures): Private sector – year 1: cervical cap $591, diaphragm $548, female condom $615, implant $959, injectable $436, male condom $321, OC $529, periodic absistence $542, spermicides $592, sponge $544, withdrawal $457, no method $1267. Private sector – year 5: cervical cap $2458, diaphragm $2287, female condom $2797, implant $1533, injectable $1978, male condom $1457, OC $2269, periodic absistence $2465, spermicides $2646, sponge $2427, withdrawal $2078, no method $5758. Public sector – year 1: cervical cap $346, diaphragm $326, female condom $269, implant $617, injectable $312, male condom $152, OC $394, periodic absistence $314, spermicides $345, sponge $306, withdrawal $272, no method $677. Public sector – year 5: cervical cap $1465, diaphragm $1383, female condom $1222, implant $1056, injectable $1417, male condom $689, OC $1733, periodic absistence $1428, spermicides $1549, sponge $1370, withdrawal $1234, no method $3079. Estimated annual (1st year) failure rates for women 15-19 years old: OC 5.9%, implant 0.3%, injectable 0.4%, diaphragm 23.7%, male condom 16.6%, female condom 24.8%, sponge 26.4%, spermicides 30.7%, cervical cap 26.4%, withdrawal 22.5%, periodic absistence 29.6%, no method 90%.	Not explicit cost-effectiveness ratio used; total costs are used as results themselves, as they incorporate failure rates (costs of unwanted and mistimed pregnancies) and frequency of STDs (costs of treating STDs). The cost of using no method is lower among adolescents than among all women, because teenagers are more likely than all women to terminate an unintended pregnancy, and abortions are far less expensive than births. The total costs for most contraceptive methods are slightly higher for adolescents than for all women because of teenagers' higher contraceptive failure and STD rates. Still, the sponge and the cervical cap are less costly for teenagers than for all women. The overall cost of using any of the rest contraceptive methods but the male and female condom is higher among adolescents than among all women because the higher cost of treating STDs among teenagers outweighs the lower cost of an unintended pregnancy.	• Model • US context • Costs and outcomes refer to adolescent contraceptive use, not representative of all women. • Costs and savings from adverse and beneficial events are taken into account. • Costs of treating STDs are taken into account. • Discontinuation rates are not taken into account. • A proportion of unintended pregnancies are assumed to be unwanted (if prevented now, they will never occur) and the rest are assumed to be mistimed (would occur in 2 years time). • Total costs include method costs, costs or savings from adverse and beneficial side effects, costs of treating STDs, and costs of unwanted and mistimed pregnancies.	Cost-effectiveness analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Koenig et al, 1996 USA [419]	A cohort of sexually active, low-income women (eligible for social programs). A model was used to project the 5 year costs by each contraceptive method, including method costs, failure costs, costs of side effects, and social service costs in the US.	Contraceptive methods used by (or appropriate for) low-income women: copper-T IUD, implant, injectable, diaphragm, male condom, OC, and tubal ligation.	Direct health care costs (method costs, side effects costs, failure costs) are based on Trussell et al, 1995 (using only the public payer model), with some substitutions regarding the purchase costs of contraceptives. The total costs of the 4 social programs during the first year following a single, unintended pregnancy brought to term range from $2,460 in model 2-child only to $7,336 in model 1-mother/child. By year 5, total cumulative costs range from $7,989 in model 2-child only to $22,023 in model 1-mother/child. Annual failure rates used in the model: copper-T IUD 0.42%, diaphragm 18%, implant 0.32%, injectable 0.30%, male condoms 12%, OC 3% and tubal ligation 0.17%. *Side effects rates and probabilities of outcomes of an unwanted pregnancy are based on Trussell et al, 1995.	Not explicitly presented; use of graphs. Social service costs per user for each contraceptive method: Diaphragms carry the greatest social service costs over 5 years: $1,462 in model1-mother/child; $529 in model 2-child only. Tubal ligation, implant, IUD and injectable have 5-year social service costs less than $35. OC and male condoms fall between these extremes. Use of no method results in 5-year social service costs of $2,498 in model2 and $6,906 in model 1. Health care + social service costs per user for each contraceptive method: No method costs $13,396 at 5 years in model 1-mother/child and $8,988 in model 2-child only. In year 1 of model 1, the least costly methods are the injectable ($168), OC ($169), and the IUD ($182). At 5 years, the IUD is the least costly ($237), followed by the implant ($472), and OC ($558). At 5 years the diaphragm costs £3,227 and the male condom $1,921. Tubal ligation has high initial costs, which result in fewer savings in the short term when compared with other highly effective reversible methods. In model 2-child only, the rank order of cost savings by the various methods is similar to model 1-mother/child. However, OC ($403) are slightly less costly than the implant ($458) at 5 years.	• Model • US context, viewpoint of health sector and social programs. • After term delivery, the model examines the social costs incurred for 5 years under two different perspectives: mother/child perspective and child only perspective; in this case, the model assumes that the child adds marginal costs to a family of 2 (mother and child) already receiving social benefits. • US social service costs are of limited value in the UK context, where the costs of social care are very different. • No economic/societal benefits arising from children in low income families are considered or included. • Discontinuation rates for each method of contraception are not taken into account. • Costs and savings of adverse and beneficial side effects are taken into account. • Costs are discounted at 5%. • Sensitivity analysis showed that results were sensitive to method costs and failure rates.	Cost-effectiveness analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Trussell et al, 1995 USA [420]	A cohort of sexually active women of reproductive age that use each particular method for periods of 1, 2, 3, 4, or 5 years. A model was used to project the 5 year costs and outcomes of each contraceptive method, including method costs, failure costs, and costs of side effects.	15 methods of contraception: tubal ligation, vasectomy, OC, subdermal implant, injectable contraceptive, progesterone-T IUS, copper-T IUD, diaphragm, male condom, female condom, sponge, spermicides, cervical cap, withdrawal, periodic absistence.	Average costs per person (method costs + side effect costs + costs of unintended pregnancies) for year 1 / year 1 to 5: Costs to private insurers (managed care model): copper-T IUD $498/540, vasectomy $763/764, implant $804/850, injectable $285/1290, OC $422/1784, progesterone-T IUS $449/2042, male condom $533/2424, tubal ligation $2554/2584, withdrawal $721/3278, periodic absistence $759/3450, diaphragm $852/3666, spermicide $913/4102, female condom $1072/4872, sponge $1264/5700, cervical cap $1310/5730, no method $3225/14663. Costs to Medicaid (public payer model): copper-T IUD $199/221, vasectomy $356/357, implant $496/513, injectable $192/871, progesterone-T IUS $197/897, male condom $227/1033, tubal ligation $1238/1252, OC $293/1273, withdrawal $319/1451, periodic absistence $336/1527, diaphragm $414/1780, spermicide $435/1957, female condom $446/2029, sponge $575/2591, cervical cap $613/2682, no method $1428/6490. Failure rates: vasectomy 0.04%, tubal ligation 0.17%, injectable 0.30%, implant 0.32%, copper-T IUD 0.42%, progesterone-T IUS 2%, OC 3%, male condom 12%, diaphragm 18%, withdrawal 19%, periodic absistence 20%, spermicide 21%, female condom 21%, sponge 30%, cervical cap 30%, no method 85%.	Results per person over 5 years, in the private insurance model, in comparison to 'no method': **Copper-T IUD**: net savings $14122, pregnancies averted 4.229. **Vasectomy**: net savings $13899, pregnancies averted 4.248. **Implant**: net savings $13813, pregnancies averted 4.234. **Injectable**: net savings $13373, pregnancies averted 4.240. **OC**: net savings $12879, pregnancies averted 4.100. OC dominates all other forms of reversible contraception requiring continuous user compliance except for the injectable. The top four cost-effective methods were the same in the public payer model.	• Model • US context: 2 perspectives: the managed payment model (private insurance) and the public payer model (Medicaid). • It is assumed that women remain on one method for the entire period, despite side effects and unintended pregnancies. • No discontinuations are taken into account. • The model assumes first-year failure rates of 'typical use'. • Using different use estimates (from typical to perfect use), the copper-T IUD remained the most cost-effective form of contraception. The cervical cap and sponge remained the least cost-effective methods even for perfect use. • Costs or savings of adverse and beneficial side effects are taken into account.	Cost-effectiveness analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Ortemeier et al, 1994 USA [421]	A cohort of sexually active women 18-44 years, without pre-existing medical problems. A model was used to estimate the costs and benefits per patient per day incurred by each contraceptive method, including method costs, failure costs, and costs/benefits of adverse/beneficial effects.	Hormonal contraception: DMPA (injectable), Norplant (subdermal implant), Nor-QD (progestogen-only oral contraceptive), Ortho-Novum 7/7/7 (combined oral contraceptive)	Total costs per patient per day (including method costs, costs of adverse effects and failure costs): DMPA $0.88, Norplant $1.78, Nor-QD $0.96, and Ortho-Novum 7/7/7 $1.08. Days of pregnancy prevention per annum: DMPA 306, Norplant 216, Nor-QD 311, Ortho-Novum 7/7/7 319. Benefits per patient per day (based on unwanted pregnancies averted and the protective effect for endometrial cancer): DMPA $3.75, Norplant $3.42, Nor-QD $3.75, and Ortho-Novum 7/7/7 $3.85.	Net benefits per patient per day: DMPA $2.87, Norplant $1.64, Nor-QD $2.79, and Ortho-Novum 7/7/7 $2.77.	• Model • Discontinuation rates are taken into account; days of pregnancy prevention per annum are adjusted for patient dropouts from therapy. • The net benefits or costs are estimated per patient per effective pregnancy prevention day. • Pregnancies are assumed to result in 34.6% abortions, and 65.4% live births. • Costs of adverse effects are taken into account. • Costs and benefits are not discounted.	Cost-benefit analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Chiou et al, 2003 USA [422]	A cohort of parous women desiring no more children for at least 5 years. A Markov model was used to project the 5 year costs and outcomes by method, including method costs, failure costs, costs of side effects, and costs of discontinuations, assuming that women that discontinue shift to one of the rest methods examined.	9 contraceptive methods for women: DMPA (Depo-Provera), OC, copper T 380A IUD, IUS (Mirena), cervical cap, diaphragm, female condom, spermicide and tubal ligation.	Method costs: analyzed in retail/procedure costs, not given as a total method cost. Failure costs: birth $6312.49, miscarriage $612, abortion $612, ectopic pregnancy $7458. Costs of treating side effects: amenorrhea $52.58, urinary tract infection $97.29, venous thromboembolism $4213.46, menorrhagia $42.2, hysterectomy $3199.49. Total 5 year costs: IUS $1646.20, IUD $967.40, DMPA $2194.50, OC $2578.00, tubal ligation $2611.00, diaphragm $2959,50, spermicide $3002.20, female condom $3106.50, cervical cap $3831.30. Effectiveness rates (average annual rates over 5 years; typical use): tubal ligation 99.7%, IUS 98.9%, IUD 98.5%, DMPA 98.3%, OC 96.2%, diaphragm 90%, spermicide 89.6%, female condom 89.3%, cervical cap 84.5%. Ectopic pregnancy probabilities: tubal ligation 0.33, IUS 0.50, IUD 0.03, rest of methods: 0.01. Side effects probabilities: tubal ligation: post operational complications 0.01. IUS: amenorrhea 0.2. DMPA: amenorrhea 0.4 in 1st year, 0.7 in 2nd year, 0.75 in 3rd year, 0.78 in 4th year, and 0.8 in 5th year. OC: amenorrhea 0.3, urinary tract infection 0.15, venous thromboembolism 0.00005. Diaphragm: amenorrhea 0.3. Cervical cap: amenorrhea 0.3. Rates of menorrhagia and hysterectomy are calculated for each method but not reported.	IUS dominates all methods (has greater effectiveness at lower cost) except tubal ligation. Among the remaining methods, with the exception of tubal ligation, IUD dominates. The incremental cost-effectiveness ratio between IUS and tubal ligation was $1148.57 per additional percentage point of effectiveness.	• Markov model • US context • Costs of side effects and discontinuations are taken into account • The 5-year horizon of the analysis may not reflect cost-effectiveness of the long-term methods such as tubal ligation over longer time frames. • All costs incurred after one year were discounted at 3%. No discounting of benefits. • The probability of ectopic pregnancy for each method was obtained from the literature; remaining pregnancies are assumed to result in 13% miscarriages, 40% live births, and 47% abortions. • Sensitivity analysis showed that cost effectiveness rankings for IUD and IUS did not change when “perfect use” failure rates were applied to the model. In contrast, barrier methods (spermicide, diaphragm and female condom) showed higher cost-effectiveness rankings than DMPA, OC and tubal ligation with perfect use. Cervical cap remained the least cost-effective method when either typical or perfect use failure rates were applied.	Cost-effectiveness analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Ashraf et al, 1994 USA [423]	A cohort of sexually active women of reproductive age. An economic model was used to project the 15 year costs by contraceptive method, including costs of method, of unwanted pregnancies, and of side effects.	Reversible and irreversible contraception; 8 contraceptive methods: condom, diaphragm, OC, IUD and progestin IUD, DMPA (Depo-Provera), levonorgestrel subdermal implant, tubal ligation, vasectomy.	Method costs calculated for 15 years, discounted at 5%: Vasectomy $587, tubal ligation $1281, IUD $1660, levonorgestrel implant $2118, DMPA $4115, OC $4729, condom $8050, diaphragm $11900. Failure costs: first-trimester abortion $633.93, miscarriage: $633.93, live birth: $12,812. Failure rates used in the model: condom 12.02%, diaphragm 15.07%, OC 3.61%, IUD 1st year 0.6%, then increasing up to 2.3% in 8th year, Progestin IUD 2.9%, DMPA 0.34%, levonorgestrel implant 0.20% in 1st year, 0.50% in 2nd, 1.2% in 3rd year, 1.6% in 4rth and 0.4% in 5th year, tubal ligation 0.42%, vasectomy 0.22%. *Unit costs of each side effect and rates of side effects are calculated for each method separately.	Net cost per patient per pregnancy-free year (including method costs, failure costs, costs and savings from adverse and beneficial side effects): Vasectomy $55, tubal ligation $118, IUD $150, levonorgestrel implant $202, DMPA $396, OC $456, condoms $776, and diaphragm $1147.	• Model • US context • Birth costs include infant costs for 1 year following birth. • Costs of side effects and discontinuations are taken into account. • Costs per year are based on 15 years of use; some methods carry high initial costs; the same analysis based on shorter period of time would give different results. • Unintended pregnancies are assumed to result in 43% live births, 44% elective abortions, 13% miscarriages.	Cost model	

Study	Population Study method	Intervention Details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Westfall et al, 1995 USA [424]	A theoretical cohort of 100 sexually active women of reproductive age. A model was used to project the 5 year method costs of each contraceptive method, adjusted for various continuation rates, and assuming that effectiveness rates and frequency of side effects are the same for the two methods.	Long acting reversible contraception; subdermal implant (Norplant) and injectable (DMPA).	Total costs over a 5 year period: Norplant $533, DMPA $700. Average annual costs: Norplant $107, DMPA $140. Initial costs are high for Norplant, but then costs decrease at time passes by (graph provided).	The implant is less costly than the injectable only if women use the implant for at least 48 months; when the implant is used for fewer than 48 months, the injectable becomes the less costly option. When the annual continuation rate is close to 100%, the five year cost of the implant for the hypothetical cohort of 100 women appears to be around $50,000, while the cost of injectable use is approximately $70,000. Thus, when continuation rates are relatively high, the implant is the more cost-effective option. However, the cost of the implant arises significantly as continuation rates decrease, such that if implant continuation rates fall much below 95%, injectable use becomes more cost-effective.	• Model • US context • Effectiveness rates and frequency of side effects are assumed to be the same for both methods examined. However, several continuation rates are applied to the model.	Cost-minimization analysis	

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Study	Population Study method	Intervention Details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Janowitz et al, 1994 Thailand [425]	Women visiting family planning clinics in Thailand. Comparative study; groups derived from 11 district hospitals introducing the implant and 11 control hospitals, matched in terms of contraceptive prevalence and the annual number of family planning clients.	Long acting reversible contraception; subdermal implant (Norplant) compared to IUD and injectable	Method costs: Cost of acceptance visit: Implant $25.47 IUD $2.64 Injectable: $1.45 Cost of follow-up: Implant $0.24 IUD $0.60 Injectable: $1.24 Cost of discontinuation: Implant $2.46 IUD $0.81 Injectable: N/A	Cost per couple year of protection: Year 1: Implant $28.18 IUD $4.07 Injectable: $5.17 Year 2: Implant $14.10 IUD $2.06 Injectable: $5.07 Year 3: Implant $9.41 IUD $1.39 Injectable: $5.03 Year 4: Implant $8.07 IUD $1.20 Injectable: $5.02 Year 5: Implant $5.65 IUD $0.86 Injectable: $5.00	• Thailand context • Introduction of implant in the health service • Data based on hospital records • Costs included only additional or marginal costs of services. Resources used reflected consultations associated with acceptance of the contraceptive method, follow-up and discontinuation. No costs following a contraceptive failure were included in the analysis. • Effectiveness rates were not estimated. Although results were presented as costs per couple year of protection, apparently they reflected average annual method costs.	Cost analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Phillips 2000 UK [426]	A cohort of 100 women per treatment arm (Implanon, Norplant, Mirena). A model was used to project the costs and outcomes over life time of each contraceptive method, including method costs, failure costs, and costs of discontinuations, assuming that women shift to another contraceptive method according to contraceptive usage rates in general practice in the UK.	Contraception; Implanon (subdermal implant) compared with progestogen only sub-dermal implant Norplant, and progestogen only intra-uterine system Mirena; further comparison with progestogen-only injectable DMPA, and combined pill (COC).	Total method costs per patient: Implanon £154.68, Norplant £296.4, Mirena £222.65 . Average method costs per patient (method costs adjusted for discontinuations): Implanon £230.88, Norplant £498.87, Mirena £523.18. Failure costs: birth £1043, abortion £460, miscarriage £352. Savings from pregnancies averted by the use of contraception per patient: Implanon £1544.6 (£1477.07), Norplant £2113.90 (£1939.89), Mirena £1891.63 (£1218.84). Pregnancy rates: Implanon 0%, Norplant 0.2%, Mirena 0.2%, no method 85%. In a cohort of 100 women, over life of each contraceptive method: Pregnancies avoided: Implanon 205 (196), Norplant 281 (258), Mirena 251 (232). Miscarriages avoided: Implanon 20 (20), Norplant 28 (26), Mirena 25 (23). Abortions avoided: Implanon 78 (75), Norplant 107 (98), Mirena 96 (88). Births avoided: Implanon 107 (102), Norplant 146 (134), Mirena 131 (120).	Net savings per patient (savings from pregnancies averted – method costs): Implanon £1313.72 (£1246.19), Norplant £1615.03 (£1441.02), Mirena £1368.45 (£1218.84). An additional comparison between Implanon and DMPA shows that Implanon dominates (lower cost, higher effectiveness). Compared to COC, Implanon is more expensive (method costs per patient: COC £120, Implanon £230.88). Using a failure rate of 6% for COC, leads to around 18 additional pregnancies over a 3-year period, compared to Implanon, for a cohort of 100 patients. The additional method costs incurred by using Implanon to avoid each additional unintended pregnancy amount to £616.	• Model • NHS perspective, 1997-98 prices. • Discontinuation rates are taken into account, but only as a result of unacceptable adverse effects. The choice of alternative method/no method in case of discontinuation is based on estimates according to contraceptive usage rates in general practice in the UK. • Unwanted pregnancies are assumed to result in 52% term births, 38% abortions and 10% miscarriages. • Failure costs and benefits are discounted at 5%. Method costs are not discounted. • Costs of side-effects are not taken into account; adverse effects are taken into account only as the cause of discontinuations. • No ICERs reported. The average cost is not as useful as the marginal cost in this context. • One-way sensitivity analyses examined different management approaches, failure rates, and discontinuation rates. In all scenarios, Implanon remained the most cost-effective of LARCs examined.	Cost-effectiveness analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
McGuire et al, 1995 UK [427]	A cohort of sexually active women of reproductive age. A model was used to estimate the NHS costs of contraception and savings from pregnancies averted.	Main contraceptive methods available in the UK: COC, IUD, injectable, implant, diaphragm/cap, condom, spermicide, vasectomy, sterilization.	Method costs: GPs: OC £39.19. Family Planning Clinics (FPCs): COC £111.43, IUD £205.10, diaphragm/cap £112.20, condom £64.29, injectable £123.71, implant £367.12, spermicide £118.95. Hospital service provision: sterilization £212, vasectomy £178. Failure costs: birth £1056.87, miscarriage £242.24, abortion £303. Number of expected pregnancies per year per 100 users: COC 2.06, IUD 2.43, injectable 0.72, implant 0.23, diaphragm/cap 13.6, condom 8.25, spermicide 19.64, vasectomy 0.18, sterilization 0.29.	Net savings per pregnancy averted: GP provision: OC £755.64. FPC provision: COC £670.05, IUD £747.41, injectable £657.79, implant £706.72, diaphragm/cap £648.08, condom £719.87, spermicide £640.05. Hospital provision: sterilization: £502.98, vasectomy: £506.44. Net savings per adjusted couple year of protection: GP provision: OC £146.30. FPC provision: OC £128.17, IUD £2805.69, injectable £141.32, implant £2722.37, diaphragm/cap £473.50, condom £64.58, spermicide £104.57. Hospital service provision: sterilization £7720.56, vasectomy £7764.68. *Net savings are compared with no method, and include method costs and NHS savings from pregnancies averted, estimated for a family with 1-2 children.	• Model • NHS perspective, 1991 prices • Pregnancies are assumed to result in 10% miscarriage, 52% live birth, and 38% abortion. These estimates regard married women with 1-2 children. • Costs of side effects and discontinuations are not taken into account. • Efficacy rates are based on average use of contraceptive methods. • GPs are assumed to provide only OC (90% of GP provision involves OC). • Costs of implant and IUD were discounted at 6% for a 5-year period.	Cost-effectiveness analysis.	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Hughes et al, 1996 UK [428]	Sexually active women of reproductive age with one or two children. Parity is assumed to affect the probabilities of outcomes of an unwanted pregnancy. A model was used to estimate the annual costs and outcomes of each contraceptive method provided by the public sector, including method and failure costs.	Contraceptive methods available in the UK and provided by GPs, Family Planning Clinics or hospitals: OC, diaphragm, IUD, condom, spermicide, injectable, implant, vasectomy, sterilization.	Method costs: Annual direct cost of GP provision (assuming provision of OC only): £39.19 Year 1 direct cost of FPC provision: OC £111.43, diaphragm £112.20, IUD £114.21, spermicide £118.95, injectable £123.71, implant £276.23, condom £64.29 (costs of IUD and implant are high initially - year 1- but are low during the following years). Cost per unit of output in the hospital sector: sterilization £212, vasectomy £178. Average cost saving from each pregnancy averted (including probabilities of miscarriage, abortion , live birth): £802.07. Effectiveness (number of expected pregnancies per year per 100 users): OC 3.00, IUD 2.00, diaphragm 18.00, condom 12.00, vasectomy 0.04, sterilization 0.17, injectable 0.30, implant 0.32, spermicide 21.00, no method 85.00. Couple year of protection: the time period provided by one unit of contraceptive cover divided by 365 days. The adjusted couple year of protection takes into account the efficacy of each contraceptive method.	GP provision (OC): • Net saving per pregnancy averted: £754.28. • Net saving per adjusted couple year of protection: £141.87. FPC provision: • Net saving per pregnancy averted: OC £666.18, diaphragm £634.61, IUD £746.73, spermicide £638.13, injectable £656.02, implant £704.97, condom £714.00. • Net saving per adjusted couple year of protection: OC £123.74, diaphragm £426.50, IUD £2768.72, spermicide £98.92, injectable £139.24, implant £2666.87, condom £59.76. Hospital provision: • Net saving per pregnancy averted: sterilization £780.30, vasectomy £783.82. • Net saving per adjusted couple year of protection: sterilization £7597.20, vasectomy £7643.17. *Net savings are compared with no method, and include method costs and NHS savings from pregnancies averted.	• Model • NHS perspective, 1991 prices. • It is assumed that unwanted pregnancies result in 23% abortions, 10% miscarriages, and 67% live births. • Costs of discontinuations and side effects are not taken into account. • Costs and couple years of protection for IUDs and implants are discounted at 6%. • One way sensitivity analysis was undertaken for the GP contraceptive provision, with various efficacy rates for OC. As the effectiveness ratio was found to be robust, no further sensitivity analyses were performed.	Cost-effectiveness analysis	

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Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
French et al, 2000 UK [125]	Sexually active women of reproductive age. Effectiveness data based on a systematic review of RCTs, controlled and uncontrolled trials (1992-1998) and meta-analysis. Comparisons were made only between options compared directly in the clinical trials pooled in the meta-analysis and only across time periods for which data were available from clinical trials pooled in the meta-analyses.	LARC: Subdermal implant (Norplant) and IUS (Mirena) compared with other reversible contraceptive methods: Norplant compared with: IUD>250mm^3, IUD≤250mm^3, OC, DMPA. Mirena compared with: IUD>250mm^3, IUD≤250mm^3.	Incremental cost=option(1)cost–option(2)cost: Norplant vs IUD>250mm^3 at 1 year: £168 Norplant vs IUD>250mm^3 at 2 years: £166 Norplant vs IUD≤250mm^3: £162 Norplant vs OC (perfect use/low cost): £173 Norplant vs OC (perfect use/high cost): £142 Norplant vs OC (imperfect use/low cost): £167 Norplant vs OC (imperfect use/high cost): £135 Norplant vs DMPA: £161 Mirena vs IUD>250mm^3 at 1 year: £89 Mirena vs IUD>250mm^3 at 2 years: £84 Mirena vs IUD>250mm^3 at 3 years: £80 Mirena vs IUD>250mm^3 at 5 years: £84 Mirena vs IUD≤250mm^3 at 1 year: £82 Mirena vs IUD≤250mm^3 at 3 years: £39 Pregnancies averted=additional risk of pregnancy with option(2) compared with option(1): Norplant vs IUD>250mm^3 at 1 year: 0.00066 (Norplant is more effective) Norplant vs IUD>250mm^3 at 2 years: 0.00315 Norplant vs IUD≤250mm^3: 0.00718 Norplant vs OC (perfect use): 0.00166 Norplant vs OC (imperfect use): 0.00830 Norplant vs DMPA: 0.00000 Mirena vs IUD>250mm^3 at 1 year: -0.00003 (IUD is more effective) Mirena vs IUD>250mm^3 at 2 years: 0.00490 Mirena vs IUD>250mm^3 at 3 years: 0.00890 Mirena vs IUD>250mm^3 at 5 years: 0.00476 Mirena vs IUD≤250mm^3 at 1 year: 0.00704 Mirena vs IUD≤250mm^3 at 3 years: 0.05301	Incremental costs per pregnancy averted: Norplant vs IUD>250mm^3 at 1 year: £255,102 Norplant vs IUD>250mm^3 at 2 years: £52,692 Norplant vs IUD≤250mm^3: £22,566 Norplant vs OC (perfect use/low cost): £104,198 Norplant vs OC (perfect use/high cost): £85,258 Norplant vs OC (imperfect use/low cost): £20,073 Norplant vs OC (imperfect use/high cost): £16,285 Norplant vs DMPA: DMPA dominates (less costly, equally effective) Mirena vs IUD>250mm^3 at 1 year: IUD dominates Mirena vs IUD>250mm^3 at 2 years: £17,205 Mirena vs IUD>250mm^3 at 3 years: £9,042 Mirena vs IUD>250mm^3 at 5 years: £17,739 Mirena vs IUD≤250mm^3 at 1 year: £11,684 Mirena vs IUD≤250mm^3 at 3 years: £721	• NHS viewpoint, 1998 UK prices. • No comparison to 'no method' The evaluation is about changing from one option to another, rather than about adopting one method compared to "do nothing" option. • Costs of side effects and discontinuations are not taken into account. • Sensitivity analysis: lower 95% CIs for pregnancy rates used in the model. ICER ranged from £13,646 to £88,103 for Norplant relative to other methods, and £635 to £34,745 for Mirena. Using upper CI values, all other methods dominated, except IUD≤250mm^3.	Cost-effectiveness analysis	
Varney & Guest, 2004 UK [429]	A cohort of sexually active women aged ≥ 30 years, starting long-term contraception A model was used to estimate annual costs	Contraception; Implant, IUS, injectable (DMPA)	Total annual costs per woman (excluding failure costs): Implant: £61.95 IUS: £41.00 Injectable: £107.16 Expected annual number of pregnancies per	The injectable was dominated by both the implant and the IUS. ICER of implant compared to IUS: £20,953 per additional pregnancy averted	• Model • NHS perspective • 2002/3 prices • Incremental analysis • Costs associated with unintended pregnancy	Cost-effectiveness analysis	

	and benefits per woman using one of the contraceptive methods evaluated. Healthcare resource use estimates for 16,835 women aged ≥ 30 years who received IUS (n=6080), implant (n=277) or injectable (n-10478) as method of contraception were derived from a GP database. Resource use included GP & practice nurse visits, and referrals to a gynaecologist outpatient clinic. Some costs were associated with side effects & discontinuation. Costs of side effects requiring additional treatment not included. Costs related to switching to other methods after discontinuing not included. Resource use related to unintended pregnancy due to contraceptive failure not considered. Effectiveness rates based on a published review.		woman: Implant: 0 IUS: 0.0010 Injectable: 0.0030		not included. • Resource use was collected for 5 years for IUS, 2 years for the implant, and 12 weeks for the injectable; total costs were annualized. • Costs discounted at 3.5% • Costs of side effects & discontinuation taken into account only partially (reflected in resource use estimates). • Discontinuation for the injectable within one year of use assumed to be zero. • Costs associated with unintended pregnancy due to contraceptive failure not included. • Savings due to non-contraceptive benefits not considered. • Probabilistic sensitivity analysis: Probability of injectable being dominated by IUS: 98% Probability of injectable being dominated by implant: 92% Probability of the ICER between implant and IUS being over the cost of an unintended pregnancy (£912): 81%		

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