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

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

Commissioned by the National Institute for Clinical Excellence

1st Draft guideline

03 March 2005

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Guideline Development Group membership and acknowledgements

Guideline Development Group

(NICE to add before second consultation)

Acknowledgements

(NICE to add before second consultation)

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Anglesey Local Health Board
Ashfield and Mansfield District PCTs
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Association of Surgeons of Great Britain and Ireland
Association of the British Pharmaceuticals Industry, (ABPI)
Barnet PCT
Bedfordshire & Hertfordshire NHS Strategic Health Authority
Bournemouth Teaching Primary Care Trust - Poole
British Association for Counselling and Psychotherapy
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British Psychological Society, The
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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
Vale of Aylesbury Primary Care Trust
Welsh Assembly Government (formerly National Assembly for Wales)
Women's & Children's Collaborating Centre

Abbreviations

AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CI	Confidence Interval
COC	Combined oral contraceptive
DFFP	Diploma of the Faculty of Family Planning and Reproductive Health Care
DMPA	Medroxyprogesterone acetate
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
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICER	Incremental cost-effectiveness ratio
IUD	Intrauterine device
IUS	Intrauterine system
LARC	Long acting reversible contraception
LSHTM	London School of Hygiene & Tropical Medcine
MI	Myocardial infarction
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NET-EN	Norethisterone enantate
NICE	National Institute for Clinical Excellence
NHS	National Health Service
NMC	Nursing and Midwifery Council
OC	Oral contraceptive pill
OR	Odds ratio
PCT	Primary Care Trust

PID	Pelvic inflammatory disease
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RR	Risk ratio
POC	Progestogen only oral contraceptive
POICs	Progestogen only injectable contraceptives
POIUS	Progestogen only intrauterine system
POSDIs	Progestogen only subdermal implants
SD	Standard deviation
STI	Sexually transmitted infections
STIF	Sexually transmitted infections foundation course
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
UKSPR	UK 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.

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

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.

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.

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.

Menorrhagia Excessive or prolonged menstrual bleeding.

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.

Oligomenorrhoea Reduction in the frequency of menstrual bleeding.

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.

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.

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.

Power See statistical power.

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.

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 administration 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 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 progesterone-only pills are also not included. Post-coital or emergency contraceptive methods including coil 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 specialists 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 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 the range of methods available as an integral part of broader sexual health services, is an essential

element 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].

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.

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, thus 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.

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. For issues of therapy or treatment, the highest possible level of evidence (EL) is a systematic review or meta-analysis of RCTs [EL=1+] or an individual RCT [EL=1-]. 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. The results of meta-analyses that were performed specifically for this guideline are also presented in Appendix B.

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 appropriate 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 9.

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 the comparisons relevant to the scope of the analysis. 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.

The economic evidence resulting from this analysis was used by the GDG in drafting their recommendations for the availability of LARC methods in the NHS. A summary of the economic evidence for each LARC method is presented at the end of the relevant chapters.

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

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.

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 first draft of the guideline that is available for stakeholder consultation.

2. Summary

2.1 Key recommendations

Contraceptive provision in the UK

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. [GPP]

Counselling and provision of information

2.1.2 Women considering a LARC method 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
- non-contraceptive benefits
- the procedure for initiation and removal/discontinuation
- duration of use
- when to seek help while using the method. [GPP]

Training of health professionals in contraceptive care

2.1.3 All healthcare 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 [GPP]

2.1.4 All healthcare 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. [GPP]

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

2.2 Summary of recommendations

Chapter 3 Contraception and principles of care

3.1 Normal fertility

Women and men should be aware that unprotected sexual intercourse risks pregnancy especially when it occurs in the days leading up to ovulation. [C]

3.2 Contraceptive provision in the UK

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

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

3.5 Counselling and provision of information

Women and men should be given accurate and detailed information, including written information, about their chosen method of contraception. [B]

Women considering a LARC method 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

- non-contraceptive benefits
- the procedure for initiation and removal/discontinuation
- duration of use
- when to seek help while using the method. [GPP]

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

For women whose first language is not English, Written information about contraceptive methods should be available in their native language. [GPP]

3.6 Contraceptive prescribing

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

3.7 Acceptability

Women should be provided with the method of contraception which is most acceptable to them. [GPP]

3.11 Contraception and sexually transmitted infection

All healthcare professionals providing contraceptive advice should promote safe sex. [GPP]

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

3.12 User autonomy and consent

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

3.16 Training of health professional in contraceptive care

All healthcare 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 [GPP]

All healthcare 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. [GPP]

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

Chapter 4 Copper intrauterine devices (IUDs)

4.1 Introduction

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

4.2 Effectiveness

Clinicians should be aware that the T-Safe Cu380A is the copper IUD of choice because of its effectiveness and duration of action. [B]

Women should be informed that modern IUDs are very effective. Pregnancy rates over 5 years are less than 2 in 100 women. [C]

4.3 Expulsion

Women should be advised that an IUD may be expelled but that this occurs in fewer than 1 in 20 women.[C]

Women should be advised to check for the presence of the IUD threads regularly with the aim of recognising expulsion. [GPP]

4.4 Discontinuation and reasons for discontinuation

Health professionals 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. [B]

4.5 Adverse effects

Clinicians should be made aware of the risk of heavier bleeding and/or dysmenorrhea with IUD use. [B]

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

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

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

4.6 Common symptoms and complaints

Women should be informed that the use of the IUD does not affect weight. [B]

Woman should be advised that the IUD does not affect mood or libido. [B]

4.7 Risks

Clinicians should follow current national guidance, such as that provided by the British National Formulary or Faculty of Family Planning & Reproductive Health Care for the prevention of infective endocarditis. [GPP]

Women with a previous ectopic pregnancy are at increased risk of future pregnancies being outside the uterus. However, these women should be reassured that the risk while using copper IUD is extremely low. [C]

Women should be advised that in the event of method failure the risk of ectopic pregnancy is less than 1 in 500. [C]

Women who present with an copper IUD failure should have an ectopic pregnancy excluded. [GPP]

The presence of actinomyces-like organisms on a cervical smear in a woman with a current copper IUD requires no action unless pelvic infection is suspected. [GPP]

Women may be informed that the chance of developing pelvic inflammatory disease as a result of copper IUD use is very low. [C]

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

Women should be informed of the small risk of perforation at the time of IUD insertion and advised on symptoms warranting early review. [GPP]

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

If the pregnancy is intrauterine and if the IUD can be easily removed it should be. [GPP]

4.8 Return to fertility

There is no evidence for any delay in return of fertility following removal or expulsion of copper IUD. [C]

4.9 Details of method use

A healthcare worker 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 as appropriate. [GPP]

Women should be informed that the position of the uterus within the pelvis or the position of a framed IUD within the uterine cavity does not influence failure rates or expulsion.[C]

Copper IUDs can be inserted from 4 weeks post partum irrespective of the mode of delivery. [GPP]

4.10 Training of health professional

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

4.11 Specific groups

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

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

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

Women should be informed that women who are HIV positive can use copper IUDs. [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. [GPP]

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

Chapter 5 Progestogen only intrauterine system (POIUS)

5.1 Introduction

The main mechanism of action of the LNG-IUS as a contraceptive is to prevent implantation. Women should be advised that LNG-IUS as a contraceptive may act predominantly to prevent implantation and may not always prevent fertilisation. [GPP]

LNG-IUS can be used as a long-term contraceptive and requires replacement every 7 years. [GPP]

5.2 Effectiveness

Women should be informed that there is a very small pregnancy rate (less than 5 women out of every 1000 users at the end of 5 years) associated with the use of LNG-IUS. [B]

5.3 Expulsion

Women should be advised that fewer than one in ten women will experience expulsion of LNG-IUS over a 5-year period. [C]

5.4 Discontinuation and reasons of discontinuation

Women should be advised that the most common side effects that lead to discontinuation of LNG-IUS use are:

- bleeding problems
- pain

The less common side effects are:

- hormone-related
- pelvic inflammatory disease. [B]

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, sometimes six months. [GPP]

5.6 Common symptoms and complaints

Women should be informed that there is some evidence of body weight change in LNG-IUS users when compared with users of IUDs and that if it occurs, it is small and not a common reason for discontinuation. [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 an increased risk for developing acne, which may lead to requests for discontinuation of the LNG-IUS. [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. [GPP]

5.7 Risks

Women with a history of venous thromboembolism (VTE) or who are at risk of VTE may use LNG-IUS, however an alternative method should be considered if VTE occurs during use. [GPP]

Women should be advised that LNG-IUS prevents ectopic pregnancies. However, in the event of a method failure ectopic pregnancy should be excluded. [GPP]

Women with a history of previous ectopic pregnancy are at increased risk of future ectopic pregnancies. However, these women should be reassured that the risk of pregnancy, and therefore an ectopic pregnancy, while using the LNG-IUS is extremely low. [B]

Women may be informed that the chance of developing PID following LNG-IUS insertion is very low at less than 1% over 1 year. [B]

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

5.8 Return to fertility

Women should be informed that return to fertility after removal of LNG-IUS is no different from that of users of the copper IUD, and appears to equate to the UK background fertility rate at 1 year. [B]

5.9 Details of method use

A healthcare worker fitting an 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. [GPP]

Women with identified risks associated with uterine or systemic infection should have investigation, appropriate prophylaxis or treatment instigated prior to insertion of the LNG-IUS. [GPP]

5.11 Specific groups

Women should be informed that LNG-IUS can be safely used by breastfeeding mothers. [GPP]

Emergency drugs including anticonvulsant medication should be available at the time of fitting a LNG-IUS in a woman known to be epileptic because there may be an increased risk of a fit at the time of cervical dilation. [GPP]

The LNG-IUS is a safe and effective method of contraception for women who are HIV positive or have AIDS. [GPP]

5.13 Drug interactions

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

Chapter 6 Progestogen only injectable contraceptives (POICs)

6.2 Effectiveness

Women can be advised that POICs have very low pregnancy rates, no higher than 4 in 1000 at 2 years. DMPA (Depot medroxyprogesterone acetate) pregnancy rates are lower than NET-EN (Norethisterone enanthate). [C]

6.3 Discontinuation and reasons for discontinuation

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

Clinicians should know that as many as half of the women using DMPA discontinue by 1 year. [C]

6.4 Adverse effects

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

- it is more likely with DMPA than NET-EN
- it is more likely as time goes by
- it is not harmful. [C]

6.5 Common symptoms and complaints

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 advised that the use of DMPA is not associated with headaches. [C]

6.6 Risks

Clinicians should know that DMPA, and probably NET-EN, are safer than oestrogen-containing contraceptives for women who have arterial or venous risk factors. [GPP]

All women should be advised that the use of DMPA is associated with a small loss of bone mineral density perhaps not all of which is recovered when the method is stopped. [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 be appropriately informed and supported in their choice. [GPP]

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

6.7 Return to fertility

Women should be told that there is likely to be a delay of up to 1 year in the return of fertility after discontinuation of POICs. [C]

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

6.8 Details of method use

POICs may be started up to and including the fifth day of the menstrual cycle. No additional contraceptive protection is needed. POICs 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. [GPP]

Repeat injections of DMPA should be given every 12 weeks and for Noristerat every 8 weeks. [B]

Women attending up to 2 weeks late may be given either injection if it is reasonably sure that they are not pregnant. [GPP]

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

6.10 Specific groups

Caution should be used in recommending DMPA to adolescents and women aged over 35 but in general the benefits outweigh the risks. [GPP]

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

Breastfeeding women may be advised that they can use POICs before the sixth week after childbirth if other methods are unacceptable.[C]

6.11 Medical conditions and contraindication

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

There is no evidence to suggest a causal relationship between the use of DMPA and an increased risk of STI (Sexually transmitted infections) or HIV acquisition. Women at increased risk of STI including HIV 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 POICs is recommended. [GPP]

6.12 Drug interactions

It is not considered necessary to avoid the use of POICs in those taking liver enzyme-inducing medication or to reduce the injection interval. [GPP]

Chapter 7 Progestogen only subdermal implants (POSDIs)

7.2 Effectiveness

Women should be advised that subdermal implants have very low pregnancy rates (less than 1 in 1000). [B]

7.3 Discontinuation and reasons for discontinuation

Providers should be aware that up to one third of women will discontinue Implanon within 2 years because of irregular bleeding. Less than 1 in 10 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 irregular 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]

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

7.5 Commond symptoms and complaints

Women should be informed that the use of Implanon is not associated with a significant change in weight. [C]

Women should be informed that the use of Implanon is not associated with significant adverse mood changes. [C]

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

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 reassured that there is no evidence for

a teratogenic effect of Implanon. Nevertheless, should pregnancy occur and be continued, the implant should be removed. [GPP]

7.7 Return to fertility

The use of contraceptive implants does not impair fertility on discontinuation. [C]

7.8 Details of method use

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

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. [C]

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

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

7.11 Medical conditions and contrindication

Implanon is not contraindicated for women with diabetes. [C]

7.12 Drug interactions

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

7.13 Follow-up

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

2.3 Future research recommendations

Despite the vast and expanding literature in contraception research, the understanding of the relative efficacy of methods is limited. There is also a scarcity of research data to inform clinicians on patterns of contraceptive use in the UK population. Multicentre studies to assess contraceptive behaviour in the UK are needed. The Guideline Development Group recommends research in the following areas:

- Typical use effectiveness of all contraceptive methods over time among UK women
- Continuation rates and patterns of contraceptive method switching among UK women
- Factors which influence initiation, continuation and effective use of contraception among UK women / couples
- Effect of non-contraceptive health benefits on uptake and continuation of contraceptive methods and on use of NHS resources

- Effect of health harms (side effects and risks) on uptake and continuation of contraceptive methods and on use of NHS resources

Other 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.

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.[16][EL=3] Most pregnancies can be attributed to sexual intercourse during a 6-day period ending on the day of ovulation,[17;18][EL=3] with the highest estimated conception rates associated with intercourse 2 days before ovulation.[19][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.[20;21]

The conception rate per menstrual cycle is known as fecundability. Natural female fertility declines with age.[22][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.[23;24][EL=3]

03.03.05

Recommendation:
Women and men should be aware that unprotected sexual intercourse risks pregnancy especially when it occurs in the days leading up to ovulation. [C]

3.2 Contraceptive provision in the UK

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.[25]

Since 1972 contraception has been provided free of prescription charges in the UK. It is provided by general practitioners, community (NHS) family planning clinics (FP) and, in recent years, in some not-for-profit charitable clinics such as Brook Advisory Centres (usually limited to young people under 25). 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 FP clinic. Not all GPs are competent to fit intrauterine devices (or systems) or contraceptive implants. Women attending FP clinics are more likely to use a long acting method of contraception than those attending 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 payment of $50 for each year they kept it.[26] 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 influences the choices made by the users.[27] If women/couples are not informed about all available methods of contraception, their choices are restricted.

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

Women requiring contraception should be provided with information and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. [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 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.[28] In the UK 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.[29] 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[30] 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.[31]

Despite the widespread use of contraception, unintended pregnancy is common. In England and Wales the abortion rate in 2003 was 17.5 per1000 women of reproductive age. The abortion rate was highest at 31.4 per 1000 for women in the 20-24 age group. The under-16 abortion rate was 3.9 per 1000.[32] 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.[33] 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.[34-36]

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.[37] 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.[38] The effectiveness of a contraceptive depends on its mode of action and how easy it is to use.[39] 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 methods 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.[40] 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).[37] 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.[41]

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).[42] 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 fall pregnant early after starting use of a method.[38] 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[43] 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 trails 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.[44;45]

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,[46] Norplant[47] and patches.[48] Body weight may also influence bleeding patterns; women with a low body weight are more likely to experience amenorrhoea while using Norplant.[49] 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 utilisation of contraception depends 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.[50] The ultimate goal of contraceptive counselling is to allow women and men to choose a method they feel most comfortable with and will continue using. Contraceptive counselling helps to determine what the woman knows about contraception and combat 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.[51][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.[52][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.[44][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 the 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%).[45][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).[53][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.[54][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).[55][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 in the group. 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.[56][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.[57][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.[58][EL=3]

Recommendation:
Women and men should be given accurate and detailed information, including written information, about their chosen method of contraception. [B]

Women considering a LARC method 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**
- **non-contraceptive benefits**
- **the procedure for initiation and removal/discontinuation**
- **duration of use**
- **when to seek help while using the method. [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.[59][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.[60][EL=3]

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

For women whose first language is not English, written information about contraceptive methods should be available in their native language. [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-convulsants 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).[61] Using

evidence-based systematic reviews,[62] 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[49] 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.[62] The document has been adapted by the FFPRHC for use in the UK[63] 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.[64]

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.[62] 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 SPR 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 if only if the history suggests that there is a risk that the woman might be pregnant.

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

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.[54]

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. 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.[65]

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.[54]

The current uptake of long-acting reversible contraception in the UK 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.[66][EL=3] Important reasons for choosing a contraceptive included: how well it works[51;56;57], ease of use and protection against STI and HIV.[57] Contraceptive choice is strongly influenced by the providers' 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[67], 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. [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)[37] 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.[27] 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.[39] 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.[68][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).[69] 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[37], 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 within weeks).[27] 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.[29]

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.[70]

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).[71] Switching to a less effective method is common.[72] 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 STI 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 are 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.[73] (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 healthcare professionals providing contraceptive advice should promote safe sex. [GPP]

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

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.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use	
Method	**Typical Use[1]**	**Perfect Use[2]**
(1)	(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
No method[4]	85	85
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.

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.[74][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)[75]

Reproductive and sexual health care including family planning services and information is recognised as 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 informed choice of contraceptive methods.[49]

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.[76-79][EL=4]

Recommendation:
Women (couples) should have freedom of choice in contraceptive methods. [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.[80]

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.[81]

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.[82]

3.14 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 patient'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.[80;83]

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 patients' 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.[84]

The Mental Capacity Bill (which as of January 2005 is still being debated in Parliament) will define what is meant by capacity and clarify the law on who can make decisions on behalf of people judged to lack capacity.

3.15 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. 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 disabled women. These factors need to be taken into consideration when discussing contraception with women with disabilities.

3.16 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 primary care. 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 reorganisation 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 primary care, 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.[85] The RCN recommends that all nurses working in primary care, 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 competence to practise. Training guidance is available from the RCN for nurses working in this field on the following: contraception and sexual health in primary care,[86] fitting intrauterine devices,[87] and inserting and/or removing subdermal implants.[88] 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 through 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.[89] 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 are adequately equipped to provide level one services in primary care and accurate contraceptive advice in secondary care.

Recommendations:

All healthcare 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 [GPP]**

All healthcare 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. [GPP]

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

3.17 Features common to progestogen only methods

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

Contraception can be broadly divided into two large categories, hormonal and non-hormonal. There are two categories of hormonal contraception, combined and progestogen only. Included in the category of LARC are the copper intra-uterine 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.

3.17.1 Progestogen only contraception

Progestogen only contraception (POC) is available in a variety of delivery systems. The injectable preparations deliver a high dose of hormone, while the oral preparation, implants and intrauterine systems deliver much lower doses.

3.17.2 Mode of action

The mode of action depends on the dose of hormone. High 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.

3.17.3 Side effects

3.17.3.1 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 supression 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 (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.

3.17.3.2 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,

3.17.3.3 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.

3.17.3.4 Ectopic pregnancy

Ectopic pregnancy is listed in many older textbooks as a side effect of the POP 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.

3.17.3.5 Cancer

In the large meta- analysis reporting a relative risk of 1.24 for use of the COC[90], 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[91] 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.

3.17.3.6 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.[92] An association between VTE and progestogen used for the treatment of gynaecological conditions such as anovulatory dysfunctional uterine bleeding[93] 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[94] may be due to observer bias.

3.17.3.7 Gall bladder disease

A weak association between use of Norplant and gall bladder disease[94] has been described but there is no evidence of any association with other POC.

3.17.3.8 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 high doses of progestogen suppressing ovarian activity and causing hypoestrogenism and there have been concerns that their use may increase the risk of osteoporosis.[95] However over the benefits in terms of pregnancy prevention with this easy to use method outweigh any theoretical concerns. While there may be a case for caution in prescribing DMPA to women with known existing risk factors for osteoporosis, there is no evidence to support the use of add-back estrogen which makes it an expensive and complicated method of contraception unsuitable for women with contraindications to estrogen.

3.17.3.9 Return to fertility

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

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methods.

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).[96]

Seven 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 CuT-380A), Multiload® Cu375, Multiload® Cu250, Multiload® Cu250 Short, Nova-T® 380, Flexi-T® 300, and GyneFix® (details of IUDs in table 5.1). 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 but is considered in a separate chapter (see Chapter 5).

4.1.2 Mechanism of action

IUDs prevent pregnancy by impairing gamete viability at fertilization and thay have a strong inhibitory effect on implantation.[97;98] Copper ions enhance these effects.[97-101][EL=3]

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

4.1.3 Use in the UK

In 2003/4, it was estimated that 4% of women aged 16-49 years in the UK 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 3 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.[102;103]

RCT data suggest that the CuT380A 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 CuT380A and the CuT220 at 8-, 10- and 12-years of use. Pregnancy rates per 100 women were significantly lower for the CuT380A at all time points (2.2 per 100 at 8-, 10- and 12-years). No pregnancies were reported among women using the CuT380A after 8 years of use.[104] (See 4.2) The Gyne T380 is no longer available in the UK but women with this device may continue to use for its 10-year licensed duration.

Multiload versions containing lower amounts of copper are licensed for three years.[102] Results from three randomised trials suggest that the efficacy of the Multiload Cu375 is at least two to three years.[105-107] (See 4.2)

The GyneFix is licensed for 5 years.[102] 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.[102;103;108] Although no studies based on IUD devices currently licensed within the UK have been undertaken to support this practice, the GDG supports this recommendation.

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. [GPP]

4.1.5 The evidence

IUDs that are not presently licensed for use in the UK are not covered in this guideline and include: CuT220C, Gyne T380, Lippes Loop®, Copper 7, Cu-Fix®, FlexiGard®, Nova® T200.

One systematic review[109] (n=19 RCTs and 11 cohort studies) was identified which assessed the effectiveness of copper IUDs versus other forms of reversible contraceptives. We examined the studies reviewed and included those which met the selection criteria as determined by the Guideline Development Group.

4.2 Effectiveness

4.2.1 Framed IUDs: Multiload Cu375 verses CuT380A

One RCT undertaken in Nigeria (n=200) reported no difference in pregnancy rates among women using Multiload Cu375 (n=100) compared to women using CuT380A (n=100) (0.0 versus 1.1 per 100 women years at 1 year).[110][EL=1+]

A multicentre RCT reported no difference in pregnancy rates among women using Multiload Cu375 (n=740) compared to women using CuT380A (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).[105;111][EL=1+]

Another RCT reported a significantly higher pregnancy rate in women using Multiload Cu375(n=948) than women using CuT380A (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).[112][EL=1+]

A multicentre RCT did not detect a difference in the pregnancy rates among women using Multiload Cu375 (n=1832) compared to women using CuT380A (n=1823) in the first year (1.2 versus 0.8 per 100 women years). However, the pregnancy rate was significantly different at 2 and 3 years (2.2 versus 1.4 per 100 women years at 2 years; 2.9 versus 1.6 per 100 women years at 3 years).[113][EL=1++]

We carried out a meta-analysis to produce a summary estimate of effectiveness from these four studies. Women using Multiload Cu375 were found to have a higher pregnancy rate than women using CuT380A at 1 year (RR 1.75 95%CI 1.04, 2.93), 2 years (RR 1.83 95%CI 1.23, to 2.72 and 3 years (RR 1.90 95%CI 1.24, 2.90). (Figure B.1 in Appendix B).

Summary of evidence

- **Women using the Multiload Cu375 had a higher pregnancy rate compared with women using the CuT380A over 3 years.**

4.2.2 Framed IUDs: Multiload Cu250 verses CuT380A

An RCT in Thailand reported no difference in the pregnancy rates among women using the Multiload Cu250 (n=715) compared to women using the CuT380A (n=681) (1.0 versus 0.2 per 100 women years at 1 year).[114][EL=1+]

One RCT in Nigeria (n=200) reported no difference in the pregnancy rate among women using the Multiload Cu250 (n=100) compared to women using the CuT380A (n=100) (0.0 versus 0.0 per 100 women years at 1 year).[110][EL=1+]

A multicentre RCT reported a significantly higher pregnancy rate in women using the Multiload Cu250 (n=1035) compared to women using the CuT380A (n=1008) (1.2 versus 0.2 per 100 women years at 1 year).[115][EL=1++]

We carried out a meta-analysis to produce a summary estimate of effectiveness from these two studies. Women using the Multiload Cu250 were found to have a higher pregnancy rate than women using the CuT380A at 1 year (RR 5.80 95%CI 1.71, 19.65). (Figure B.2 in Appendix B)

4.2.3 Nova-T 380

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.[116][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.[117][EL=3]

Summary of Evidence

- **Women using the Multiload Cu250 had a higher pregnancy rate than woman using the CuT380A in the first year.**

4.2.4 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 multicentre RCT reported no difference in pregnancy rates between women using the Cu-Fix (n=447) and women using the CuT380A (n=427) (1.0 versus 0.0 per 100 women years at 1 year and 2 years).[118][EL=1+]

A multicentre RCT comparing the CuT380A with the TCu220 (not licensed) reported a cumulative pregnancy rate of 2.2 at 8, 10 and 12 years in theTCu380A group (n=1396). All pregnancies occurred before 8 years.[104][EL=1+]

A multicentre RCT reported no difference in pregnancy rates between women

using the FlexiGard (n=2102) and women using the CuT380A (n=2184) (1.2 versus 0.6 per 100 women years at 1 year, 1.7 versus 1.1 per 100 women years at 2 years, 2.0 versus 1.7 per 100 women years at 3 years).[119][EL=1++]

An RCT reported no difference in pregnancy rates among women using the GyneFix (n=302) and women using the CuT380A (n=305) (0.0 versus 0.3 per 100 women years at 1 year, 0.0 versus 0.3 per 100 women years at 2 years, 0.0 versus 0.3 per 100 women years at 3 years).[120][EL=1+]

Another RCT reported no difference in pregnancy rates in women using FlexiGard (n=100) and women using CuT380A (n=100) (0.0 versus 1.1 per 100 women years at 2 years, 0.0 versus 2.2 per 100 women years at 4 years, 0.0 versus 3.3 per 100 women years at 6 years).[121][EL=1+]

We carried out a meta-analysis to produce a summary estimate of effectiveness from these five studies. Women using frameless devices were found to have a significantly higher pregnancy rate than women using CuT380A at 1 year (RR 2.06, 95%CI 1.11 to 3.82) and 2 years (RR 1.63 95%CI 1.01 to 2.62) However there was no difference in pregnancy rates between women using the frameless device and women using CuT380A after 3 years (RR 1.15 95%CI 0.74, 1.77). (Figure B.3 in Appendix B)

A systematic review of four RCTs [118-120;122] reported a tendency towards a higher pregnancy rates with frameless devices (Cu-Fix, Flexigard) at three years but the result was not statistically significant (RR 1.34, 95% CI 0.85 to 2.10).[123][EL=1+] One of the RCTs from this review comparing the CuT380A (n=305) with the Gynefix (n=302) in China reported a cumulative pregnancy rate of 0.34 versus 0.0 at 1, 2 and 3 years.[120][EL=1+]

4.2.5 Gynefix

A UK non-comparative study (n=138) reported no pregnancy among Gynefix users at 2 years.[124][EL=3]

One non-comparative study (n=525) in Belgium reported a cumulative pregnancy rate of 0.6 and 0.9 per 100 women among Gynefix users at 2 and 5 years respectively.[125][EL=3]

Summary of evidence

- **There was no significant difference in pregnancy rates after 3 years use comparing the frameless devices with CuT380A. (refer to Table 4.1)**

- **Table 4.1** Efficacy and duration of use of IUDs currently available in the UK [102]

Device	Shape and material	1 year Pregnancy rate	Copper content (mm^2)	Licensed duration of use (years)	Pregnancy rate: Evidence based duration (years)
Flexi-T 300	T-shaped plastic with copper wound on vertical stem. Thread attach to base of vertical stem		300	5	No studies identified
GyneFix [120;124;125]	Frameless copper tubing segments on polypropylene	0.0 to 0.6 [120][EL=1+] [124][EL=3]	330	5	0.0 (3 years) [120][EL=1+] 0.0 (2 years) [124] [EL=3] 0.6 (2 years) [125] [EL=3] 0.9 (5 years) [125][EL=3]
Multiload Cu250 [114] [110] [115]	Plastic carrier with 2 down curving arms, copper wound on vertical stem. Thread attach to base of vertical stem	0 to 1.2 [110;114] [115][EL=1+]	250	3	Data available for 1 year only
Multiload Cu250 Short	Plastic carrier with 2 down curving arms, copper wound on vertical stem.		250	3	See above. (MLCu250 long or short not differentiated in studies identified)

	Thread attach to base of vertical stem				
Multiload Cu375 [105;110-113]	Plastic carrier with 2 down curving arms, copper wound on vertical stem. Thread attach to base of vertical stem	0.0 to 1.2 [105;110-113] [EL=1+]	375	5	1.3 to 2.7 (2 years) [105;111;112] [EL=1+] 1.8 to 2.9 (3 years) [105;111;113] [EL=1+]
Nova-T380 [116;117]	T-shaped plastic with copper with silver core wound on vertical stem. Threads attach to base of vertical stem (distribution of the Nova-T200 in the UK ceased in October 2001)	0.5 to 0.8 [116;117] [EL=3]	380	5	1.6 (2 years) [116;117] [EL=3] 2.0 (3 years) [116] [EL=3] 2.0 (4 years) [116] [EL=3] 2.0 (5 years) [116] [EL=3]
T-Safe CU 380 A (CuT380A) [110;126] [105;111] [112;113] [114;118] [119;120] [104;121] [127;128]	T-shaped plastic with copper wound on vertical stem and on each horizontal arm. Threads attach to base of vertical stem	0 to 1.4 [126] [EL=2+] [105;110;111] [112-114] [118-120] [EL=1+]	380	8	0.0 to 1.4 (2 years) [105;111;118] [112;113;119] [120;121] [EL=1+] 0.3 to 1.7 (3 years) [105;111;119] [120] [EL=1+] 1.4 to 2.2 (4 years) [121;128] [EL=1+] 2.0 to 3.3 (6 years) [121;127] [EL=1+] 1.4 (7 years) [128] [EL=1+] 2.2 (8 years) [104] [EL=1+] 2.2 (10 years) [104] [EL=1+] 2.2 (12 years) [104] [EL=1+]

Recommendation:

Clinicians should be aware that the T-Safe Cu380A is the copper IUD of choice because of its effectiveness and duration of action. [B]

Women should be informed that modern IUDs are very effective. Pregnancy rates over 5 years are less than 2 in 100 women. [C]

4.2.5 Copper IUDs versus other contraceptive methods

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(See 5.2.2)

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 380Ag users respectively at 7 years.[128][EL=1-] Results of this RCT were documented in fourother reports during the 7 years study period.[129-133]

One RCT compared IUS-20 (n=141) and Nova T IUD (n=136) (formerly Novagard, copper surface 200) in Finland and Brazil and reported a pregnancy rate of 1/5495 women months and 7/5176 women months respectively at 5 years.[134][EL=1-] Results of this RCT were documented in 3 other reports during the 5 years study period.[135-137]

One European multicentre RCT compared IUS-20 (n=1821) and Nova T IUD (n=937) (formerly Novagard, 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.[138;139][EL=1-] Results of this RCT were documented in two other reports during the 5-year study period.[140;141]

Interim results from the WHO international muticentred RCT (n=3815 insertions) showed a significant difference in cumulative pregnancy rates between LNG-IUS users (n=464) and TCu380A IUD users (n=580) at 6 years (0.5 versus 2.0).[127][EL=1-]

A cohort study in East Africa compared women using CuT380A (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).

(See 6.6.2)
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.[126][EL=2+]

Summary of evidence

- **Although there is some evidence to suggest that the IUS may be more effective than a copper IUD containing 380mm Cu, 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 CuIUDs 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.[99][EL=4] 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.

4.3.1 Copper IUDs

A systematic review[123] of four clinical trials[118-120;142] compared GyneFix, Cu-Fix (not licensed in the UK), Flexigard (not licensed in the UK) and T-Safe Cu380A, with expulsion as one of the outcomes assessed. The three studies excluded nulliparous women. One of the RCTs from this review comparing CuT380A (n=305) versus Gynefix (n=302) in China reported a discontinuation rate due to device expulsion of 4.63 versus 2.67 at 1 year. The corresponding figure for 3 years was significantly different at 7.38 versus 3.00.[120][EL=1+]

RCTs comparing the CuT380A to other IUDs (MLCu375, MLCu250) reported expulsion rates ranging from 2.4% to 4.5%.[110;113;143][EL = 1+]

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.[116][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. [117][EL=3]

4.3.2 Copper IUDs versus other contraceptive methods
(See 5.3.2)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu 380A 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).[128-132][EL=1-]

An RCT compared IUS-20 (n=141) and Nova T IUD (n=136)(copper surface 200) in Finland and Brazil. It reported cumulative continuation 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).[134-137][EL=1-]

One European multicenter RCT which compared IUS-20 (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.[138-141][EL=1-]

Interim results from the WHO international multicentred RCT (n=3815 insertions) reported no significant difference between LNG-IUS users (n=464) and TCu380A IUD users (n=580) in discontinuation rates due to expulsion (7.6% versus 8.3%) at 6 years.[127][EL=1-]

A multi-centred study undertaken mainly in developing countries that stratified reasons for discontinuation by population characteristics such as age, education, religion, and breast feeding suggested that women <20 years of

age had significantly higher rates of expulsion during the first year of use compared to women aged over 35 years (8.2% versus 1.8%).[144][EL=3]

Recommendation:
Women should be advised that an IUD may be expelled but that this occurs in fewer than 1 in 20 women. [C]

Women should be advised to check for the presence of the IUD threads regularly with the aim of recognising expulsion. [GPP]

4.4 Discontinuation and reasons for discontinuation

(See 3.10)

4.4.1 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.[99;116] RCTs comparing the CuT380A to other IUDs (MLCu375, MLCu250) reported rates for removal due to bleeding and/pain ranging from 3.8% to 7.3% at one year of use.[110;113;143][EL=1+]

(See 4.7.4.1)

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 were 1.9, 3.4, 4.5, 5.5 and 7.1 and due to PID was 0.9 throughout the 5 years.[116][EL=3]

Another non-comparative study (n=400) in Finland reported a cumulative discontinuation rate of 11 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.[117][EL=3]

A multi-centred study undertaken mainly in developing countries that stratified reasons for discontinuation by population characteristics such as age, education, religion, and breast feeding reported a cumulative total discontinuation rate at 12 months of 13.3% The 12 month discontinuation rate due to expulsion was 3.1%, for personal reasons was 4.3 % and for bleeding/pain was 4.5%.[144][EL=3]

4.4.2 Frameless IUDs

A systematic review of 3 RCTs reported no difference in removal rates due to excessive bleeding among parous women who used either the frameless copper IUDs (Cu-Fix, FlexiGard, both unlicensed, and GyneFix) or the CuT380A (RR 0.92, 95% CI 0.74 to 1.14). No differences were identified in rates of removal for bleeding alone or for bleeding with pain between the two groups.[123][EL=1+]

4.4.3 Copper IUDs versus other contraceptive methods

(See 4.7.4.2 and 5.4.2)

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 TCu 380Ag 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 (1.0% versus 0.9% , 1.3% versus 1.5%, and 3.6% versus 3.6% at 1, 2 and 7 years respectively).[128-132][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.[134-137][EL=1-]

One European multicenter 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.[138-141][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.[127][EL=1-]

Summary of evidence

The commonest reason for discontinuation of copper IUDs is bleeding problems. Over 5 years of use, between 1 in 4 and 1 in 2 women will stop using the method.

Recommendation:

Health professionals 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. [B]

4.5 Adverse effects

4.5.1 Bleeding problems

(See 4.4)

It has been reported that although IUDs do not affect ovulation, the onset of menstrual bleeding occurs earlier than normal cycles.[145]

4.5.1.1 Copper IUDs

One RCT reported no difference in the rates of menorrhagia (4% versus 5% versus
2%) among users of TCu380A (n=100), MLCu375 (n=100) and MLCu 250 (n=100) 1 year after IUD insertion. The corresponding rates for amenorrhoea were 2% versus 2% versus 1% for intermenstrual bleeding 6% versus 4% versus 4% and for dysmenorrhoea 27% versus 24% versus 21%.[110][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.[111][EL=1-]

A RCT reported no difference in the rates of intermenstrual bleeding (27.4% versus 24.4%) among users of TCu380A (n=1008) and MLCu250 (n=1035) at 1 year. The corresponding rate for dysmenorrhoea was significantly different at 49% versus 35.6%.[115][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 rates of problems comparing Tcu380A, MLCu375 and MLCu380.**

Recommendation:
Clinicians should be made aware of the risk of heavier bleeding and/or dysmenorrhea with IUD use. [B]

4.5.1.2 Copper IUDs versus other contraceptive methods
(See 5.5.1)

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 Cu T380A 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 age 30 or over using LNG-IUS were significantly less likely to complain of amenorrhoea, oligoameorrhoea and dysmenorrhoea than were younger women.[128][EL=1-] (Refer to 6.3)

Re-analyses of menstrual diaries (n=287) from one RCT[139] investigated bleeding patterns in women with post-abortal and post-menstual insertion of Nova-T IUD (likely to be formerly Novagard, copper surface 200, discontinued in 2001) and LNG-IUS. Women receiving LNG-IUS post-abortally had 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.[146][EL=1-]

4.5.1.3 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=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.[147][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.[148][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.[149][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.[150][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.[62][EL=4]

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

Women who find heavy bleeding in association with a copper IUD may consider changing to a LNG-IUS (Levonorgestrel intrauterine system). [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.[151][EL=1-] This RCT was continued for 3 years and no significant differences were reported between the 2 groups in MBL and haematological parameters.[152][EL=1-]

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

4.6 Common symptoms and complaints

4.6.1 Weight change

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

(See 4.4 and 5.6.1.2)
An European RCT reported no evidence of a difference in body weight change among women using the copper releasing Nova-T (formerly Novagard, 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%).[139][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) at 7 years.[128][EL=1-]

A 5-year multicentre controlled cohort study (n=16,021), undertaken mainly in developing countries, reported weight gain in IUD (copper and non-copper) users (n=26) and Norplant)(n=149) and sterilisation (n=0) (0.9 versus 4.5 versus 0 per 1000 women years). The figures for reported weight loss were 16 versus 39 versus 1 per 1000 women years.[94][EL=2+]

Recommendation:
Women should be informed that the use of the IUD does not affect weight. [B]

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[153] to about 30% in a national survey in the USA.[154]

(See 5.6.2.2)
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 CuT 380Ag IUD group), or depression (1.2% in the LNG-IUS group versus 1.1% in the CuT 380Ag IUD group).[128][EL=1-].

A cohort study (n=1073) reported no differences in a decrease of sexual desire between OC and IUD (MLCu375, Nova-T, Gine 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.[155][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)(n=35) compared with Norplant (n=940 and sterilisation (n=17) (1.2 versus 2.8 versus 2.2 per 100 women years). The figures for 'premenstrual tension' were 3.3 versus 1.5 versus 11.8 per 100 women years.[94][EL=2+] (refer to IUS chapter)

Recommendation:
Woman should be advised that the IUD does not affect mood or libido. [B]

4.7 Risks

4.7.1 Cardio-vascular disease

(See 6.6.2)

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 pressure between the two groups at 120 months.[156][EL=2+]

A FFPRHC guidance document advises that insertion in women with current or a history of venous thrombo-embolism is acceptable.[157][EL=4]

In the cuurent WHOMEC, copper IUDs are assigned category '2' for women with valvular heart disease. WHOMEC recommends that prophylactic antibiotics to be used at time of insertion to prevent endocarditis.[49] A small study identified transient bacteraemia from vaginal organisms in 13% of women within 10 minutes of IUD replacement/insertion.[158][EL=3]

For gynaecological procedures, it is recommended 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.

Recommendation:

Clinicians should follow current national guidance, such as that provided by the British National Formulary or Faculty of Family Planning & Reproductive Health Care for the prevention of infective endocarditis. [GPP]

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.[159] Ectopic pregnancy rate in women generally increases with age, however IUD failure rates decline with age.

4.7.2.1 Copper IUDs

A secondary analysis of a number of studies estimated absolute annual ectopic pregnancy rates of 0.02 per 100 CuT 380 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 CuT 380 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 TCu380 and MLCu375 users at 2 years. The figure was 0.4 ± 0.3 for MLCu250 users.[97;160][EL= 3]

One RCT reported no ectopic pregnancy among users of TCu380A (n=1823) and MLCu375 (n=1832) during the first year of use. Cumulative discontinuation rates due to ectopic pregnancy were 0.2 versus 0 per 100 woman years at 2 years and 0.2 versus 0.1 at 3 years respectively.[113][EL=1++]

Another RCT reported cumulative discontinuation rates due to ectopic pregnancy of 0 versus 0.4 per 100 woman years in users of TCu380A (n=300) and CuSafe300 (n=300) at 1 year. The rates were 0 versus 0.4 and 0.5 versus 0.4 at 2 and 3 years.[161][EL=1-]

One RCT reported cumulative discontinuation rates due to ectopic pregnancy of 0 among users of MLCu250 (n=1011) versus 0.1 per 100 woman years in users of TCu380A (n=1396) at 3 years. The figures were 0.1 for TCu380A users at 5 years.[162][EL=1++]

Another RCT comparing the TCu380A (n=2184) and Flexigard (n=2102) (unlicensed) reported cumulative discontinuation rates due to ectopic pregnancy of 0.1 per 100 woman years at 1, 2 and 3 years in the TCu380A group.[119][EL=1++]

One RCT comparing TCu380A IUDs with TCu220 IUDs (not licensed) reported cumulative discontinuation rates due to ectopic pregnancy of 0.4 per 100 woman years among TCu380A users at 8 years. (Data not presented here for TCu220 users.)[104][EL=1++]

4.7.2.2 Copper IUDs versus other contraceptive methods

(See 5.7.3.2)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported 0 versus 2 ectopic pregnancies in LNG-IUS and CuT 380Ag users respectively at 7 years.[128][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.[139][EL=1-]

Interim results from the WHO international muticentred RCT (n=3815 insertions) showed a significant difference in the discontinuation rates due to ectopic pregnancy between TCu380A IUD users (n=580) and LNG-IUS users (n=464) at 6 years (0.1 versus 0.0).[127][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.[163][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 controls. IUD use prior to conception among pregnant women did not affect the risk of ectopic pregnancy.[164][EL=2-]

Recommendations:
Women with a previous ectopic pregnancy are at increased risk of future pregnancies being outside the uterus. However, these women should be reassured that the risk while using copper IUD is extremely low. [C]

Women should be advised that in the event of method failure the risk of ectopic pregnancy is less than 1 in 500. [C]

Women who present with a copper IUD failure should have an ectopic pregnancy excluded. [GPP]

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.[165-168] The role of actinomyces-like organisms in infection in IUD users is unclear.[169] They may be identified on cervical smears, but have not been shown to be predictive of any disease.[101;170-172]

4.7.3.1 Copper IUDs

IUDs users may have a higher risk of infection with actinomyces-like organisms compared to non-users. A non-comparative study of asymtomatic IUD users with untreated ALOs followed up for 2 years reported no occurrence of PID.[173][EL=3]

4.7.3.2 Copper IUDs versus other contraceptive methods

(See 5.7.4)

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).[174][EL=3] 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 smear (0% versus 0.1%) in both the LNG-IUS and the TCu380Ag IUD group.[128][EL=1-]

Previous recommendations suggested follow-up every 6 months for a woman choosing to continue using an IUD in the presence of ALO.[175][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 no action unless pelvic infection is suspected. [GPP]

4.7.4 Pelvic inflammatory disease (PID)

(See 4.4, 5.4 and 5.7.5)

There is a possibility that infective organisms may be introduced during insertion of an IUD. The possible association between IUDs and Pelvic inflammatory disease (PID) has been an important concern about the device's safety and has influenced decisions on its use.

PID is associated with upper genital tract infection typically caused by Chlamydia trachomatis and Neisseria gonorrhoeae in the UK. In the majority of women, PID remains asymptomatic. When symptoms do appear, they often include fever, pelvic pain and vaginal discharge. Among women with

PID, about 20% will become infertile and among those who conceive, about 10% of the pregnancies will be ectopic.[176]

The annual incidence of PID is estimated to be 1-2% in women of reproductive age in the US.[177] 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 previous 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).[178][EL=1-]

4.7.4.1 Copper IUDs

(See 4.4.1)

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.[116][EL=3]

4.7.4.2 Copper IUDs versus other contraceptive methods

(See 4.4.3 and 5.7.5)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu 380A users in discontinuation rate due to PID (1.0% versus 0.9% , 1.3% versus 1.5%, and 3.6% versus 3.6% at 1, 2 and 7 years respectively).[128-132][EL=1-]

One European multicenter 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.[138-141][EL=1-]

A European RCT comparing LNG-IUS (n=1821) to Nova-T (n=937) (formerly Novagard, copper surface 200) reported a significant difference in cumulative

discontinuation rates due to PID of 0·5 % versus 2·0% and 0·8% versus 2·2% respectively at 3 and 5 years.[138;139][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 (n=464) and TCu380A IUD users (n=580) at 6 years (0.3 versus 0.1).[127][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).[163][EL=2+]

An RCT and systematic review showed that women at low risk of STIs who use IUDs have a low risk of PID.[179;180][EL=1++]

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.[64][EL=1-]

4.7.4.3 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. 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).[180][EL=1+] In 2 RCTs included in this review, users of the CuT380A 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)[179] and 0.98 (95%CI 0.06 to 15.73).[181][EL=1-]

Recommendation:
Women may be informed that the chance of developing pelvic inflammatory disease as a result of copper IUD use is very low. [C]

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

4.7.5 Uterine perforation

Uterine perforation occurs in fewer than 1 in 1000 insertions.[99;182] A systematic review of 4 RCTs evaluated the effectiveness of frameless IUDs and classical IUDs. It reported no perforations (result of 2 RCTs comparing TCu380A versus FlexiGard (unlicensed in the UK), 245 nsertions).[119;120;123][EL=1+] No perforations were reported in an audit of 138 insertion of Gynefix IUDs.[124][EL=3]

A study from New Zealand of almost 17500 IUD insertions reported an incidence of perforation of 1.6 per 1000 insertions. 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.[182][EL=3] Another study, using an international dataset of over 21500 insertions, estimated the perforation rate to be 1.9–3.6 per 1000 insertions.[183][EL=3]

4.7.5.1 Copper IUDs

A non-comparative study (n=574) in the UK reported no perforations after insertion of Nova T380 at 5 years.[116][EL=3]

Another non-comparative study (n=8343) in Turkey reported an incidence of 2.2 perforation per 1000 insertions of T 380A IUD and the risk of perforation may be associated with insertion 0-3 months postpartum.[184][EI=3]

4.7.5.2 Copper IUDs versus other contraceptive methods

(See 5.7.6.2)

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 TCu380Ag users at 7 years.[128][EL=1-]

The FFPRHC endorses a 6-week interval after an asymptomatic, suspected perforation before IUD insertion is attempted again.[185][EL=4]

Recommendation:
Women should be informed of the small risk of perforation at the time of IUD insertion and advised on symptoms warranting early review. [GPP]

4.7.6 Women who become pregnant while using an IUD

Approximately 6% of pregnancies occurring in women using an IUD are ectopic.[97] IUDs should not be used during pregnancy and they are assigned category '4' by WHOMEC.[49]

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%.[186][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

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UKSPR.[64][EL=4]

Recommendations:

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

If the pregnancy is intrauterine and if the IUD can be easily removed it should be. [GPP]

4.8 Return to fertility

4.8.1 copper IUDs

A cohort study reported no difference in fertility after discontinuation of contraception in parous women using IUDs compared to women not using IUDs.[187][EL=2-] Data for *nulliparous* women from this cohort study suggested that long-term IUD use was associated with reduced fertility.[188] 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).[189]

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.[190][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).[191][EL=3]

4.8.2 Copper IUDs versus other contraceptive methods

(See 5.8)

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 (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.[141][EL=1-]

Another RCT reported a pregnancy rate of 96.4% in ex-LNG-IUS users (n=60) compared to 91.1% in ex-TCu 380Ag IUD users (n=50) at 1 year.[133;192][EL=1-]

Recommendation:

There is no evidence for any delay in return of fertility following removal or expulsion of 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. STI/HIV screening may contribute substantially to safe and effective use of IUDs, depending on the public health and/or service context.[193] Breast examination, cervical screening, routine laboratory tests, haemoglobin test and blood pressure screening are not recommended.[62;64][EL=4]

Recommendation:

A healthcare worker 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 as appropriate. [GPP]

4.9.2 Position within the uterine cavity

The anatomical position of the uterus within the pelvis (anteverted/retroverted; anteflexed) may influence the position of the IUD within the uterine cavity. It has been suggested that this may affect contraceptive efficacy.

Data was analysed from a multicentre study of 5603 insertions of various copper containing IUDs (TCu200, TCu380A, TCu380G, MLCu250 and MLCu375) among parous women with anteverted uteri (n=3135), mid-position (n=852) or retroverted uteri (n=1533). Cumulative removal rates due to pregnancy (0.6 ± 0.1 versus 0.4 ± 0.2 versus 0.7 ± 0.2 per 100 insertions) and expulsion (2.7 ± 0.3 versus 1.7 ± 0.5 versus 2.5 ± 0.4 per 100 insertions) did not differ significantly between these three groups at 6 and 12 months. The 12-month removal rate for bleeding and/or pain was significantly higher in women with mid-positioned uteri than in women with anteverted uteri (6.3 ± 0.9 versus 3.5 ± 0.4).[194][EL= 2-] No significant differences in anatomical position of the uterus were found in a nested case-contol study of copper IUD (<300 mm2 and >300 mm2; types not specified) users (n=71) who became pregnant, experienced a miscarriage, abortion or ectopic pregnancy compared to controls (n=284).This study reported a higher risk of pregnancy in women using IUDs with less than 300 mm2 copper.[195][EL= 2-]

A non-comparative study of 538 nulliparous women or women with a history of complications from previous IUD use were fitted with Gynefix and followed for one year. The expulsion rate was 6.7% (95%CI 4.4 to 9.9) and pregnancy rate 0.6% (0.09 to 2.2). Women with retroverted uteri were twice as likely to have the IUD removed compared to women with anteverted uteri (RR 2.66; 95%CI

1.09 to 6.48). Estimates were adjusted for age and experience of the health professional inserting the device.[196][EL= 2-]

A cohort study in Brazil compared women with no complaints (n=245) to women with complaints (n=236) associated with T shaped IUDs (T-Cu 200 or T-Cu 380) in use for 6 months. The study reported that complaints of bleeding and pain did not correlate with the position of the IUDs as imaged by vaginal ultrasound.[150][EL=2-]

Evidence summary

- **No evidence of difference between different framed IUDs**
- **Data for frameless IUD are insufficient to draw any conclusion.**

Recommendation:
Women should be informed that the position of the uterus within the pelvis or the position of a framed IUD within the uterine cavity does not influence failure rates or expulsion. [C]

4.9.3 Time of fitting of IUD

4.9.3.1 In a normal menstrual cycle

Having reasonably excluded pregnancy, an IUD may be inserted at any time during the menstrual cycle.[49] 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.

4.9.3.2 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. Systematic reviews show that the insertion of an IUD at the time of surgical

abortion is safe and practical.[197][EL=1-] Although is it unlikely to make a difference, these multicentre trials employed IUDs that are rarely used currently in the UK (Lippes Loop, Copper 7 and T-Safe Cu200). Expulsion rates were higher after second-trimester abortion than after earlier procedures. Delaying insertion following second-trimester termination of pregnancy (TOP) was advised, but no timescale was given.[197] Case-control studies show the risk of uterine perforation following IUD insertion within 30 days of a TOP is low[198][EL=3] and only three perforations were identified in 2348 such insertions in a WHO study.[199][EL=2-] Re-admission rates for pelvic infection were not increased by IUD insertion immediately following a first-trimester TOP.[200][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).[185][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.[49]

4.9.3.3 Post delivery

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.[49] 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.[201][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-randomised, prospective study included 734 breastfeeding women with a mean time of insertion of a T-Safe Cu380A of 47.6 days postpartum (SD 9.9). It showed an expulsion rate at 12 months of 5.6 per 100 insertions.[202][EL=2+] Women with current puerperal sepsis should be advised against insertion of an IUD.[203][EL=4]

Recommendation:
Copper IUDs can be inserted from 4 weeks post partum irrespective of the mode of delivery. [GPP]

4.10 Training of health professionals

(See 3.17)

A large prospective study, which included 17,469 Multiload Cu375 insertions by 1,699 doctors, showed that doctors inserting fewer than 10 IUDs in a six year period reported significantly more perforations than those inserting between 10 and 100 IUDs.[182][EL=2+]

A multicentre randomised trial [204][EL=1+] and a prospective cohort study[205][EL=3] support IUD insertion by any appropriately trained clinician.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 clinicians 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.[87][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 a month. [GPP]

4.11 Specific groups

4.11.1 Age

4.11.1.1 Adolescents

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

Copper IUDs are assigned category '2' for women aged from menarche to under 20 years.[49]

4.11.1.2 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.[206][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.[207][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.[208][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 ($p<0.01$).

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

4.11.2 Women with body mass index (BMI) over 30

We did not identify any studies.

In the current WHOMEC, copper IUDs are assigned category '1' for women over 30 kg/m^2 body mass index.[49]

4.11.3 Women who are breastfeeding

A cohort study reported no increase in copper levels in breast milk in breasfeeding mothers with an IUD (Cu380A and Cu200B) (n=62) inserted at 10-weeks post-partum, when compared with a third group that were not using an IUD (n=33).[209][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.[210][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

4.12.1 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.[211][EL=4]

A case series study concluded that the CuT380A is a safe and effective device for women with type 2 diabetes. Women requesting a CuT380A (n=176) were followed for 5 years at a family planning clinic in California. Participants were more likely to be obese and have already given birth. Continuation rates were high at 1- and 3-years, 93% and 70%, respectively. The pregnancy rate was 1.57% per 100 woman years and expulsion rate 1.96%.[212][EL=3]

These rates are comparable with those found in randomised studies of parous women.[213][EL=2+]

In the current WHOMEC, copper IUDs are assigned category '1' for women with diabetes.[49][EL=4]

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

4.12.2 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-convulsants.[49][EL=4]

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4.12.3 Sexually transmitted infectioins and HIV/AIDS

(See 3.11)

A prospective study which evaluated whether HIV-positive women who used IUDs were at an increased risk of complications. A total of 144 HIV-infected women and 471 non-infected women in Kenya were followed for four months after CuT380A IUD insertion. No differences in overall complications (odds ratio 0.80; 95%CI 0.38 to 1.68) or of infection-related complications (odds ratio 1.02; 95%CI 0.46 to 2.27) were found at either one or four month follow-up visits.[214;215][EL=2++]

In the current WHOMEC, AIDS as a condition is classified as category '3' for insertion and '2' for continuation unless the woman is clinically well on ARV therapy in which case, both insertion and continuation are classified as category '2'.[49]

Recommendation:
Women should be informed that women who are HIV positive can use copper IUDs. [GPP]

4.13 Drug interactions

4.13.1 Antibiotics

We did not identify any studies.

In the current WHOMEC, copper IUDs are assigned category '1' for women who are prescribed antibiotics.[49][EL=4]

4.13.2 HIV/ARV therapy

There is no known drug reaction between ARV therapy and IUD use.

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.[64][EL=4] A woman should also be advised to return at any time to discuss problems, or if she wants to change her method, or when it is time to have the IUD removed.[64][EL=4] No routine regular follow-up is required.

Recommendations:

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. [GPP]

4.14.1 Information prior to insertion

See 3.5

Recommendation:

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

4.15 Economic evidence

The economic analysis undertaken for this guideline showed that IUD dominates (i.e. it is both more effective and less costly) the injectable between 2 and 15 years of contraceptive use, which was the maximum time frame examined. For one year of use, IUD is more effective and more costly than the injectable with an Incremental Cost-Effectiveness Ratio (ICER) of £16 per pregnancy averted.

IUD also dominates the implant between 2 and 15 years of contraceptive use. For one year of use, the implant is more effective at an additional cost of £82,095 per pregnancy averted.

IUD is the dominant option compared to IUS 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 decreases over time, starting from £18,583 per pregnancy averted for 5 years of use, and falling at £1,178 and £1,889, compared to 5-year and 8-year licensed IUD respectively, 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 £59,950 per pregnancy averted.

In conclusion, IUD is more cost-effective than all other LARC methods (injectable, IUS, implant) for periods of use between 2 and 4 years. IUD is still more cost-effective than the injectable and the implant for longer periods of use. However, relative cost-effectiveness between IUD and other LARC methods is highly sensitive to changes in discontinuation rates.

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-releasing intrauterine system (LNG-IUS) consists of a polyethylene T-shaped frame, with a steroid reservoir around the 32 mm long vertical stem. The LNG-IUS has been licensed as a contraceptive in the UK since May 1995. LNG-IUS is inserted into the uterine cavity. Correct placement of the device is necessary to deliver the steroid over the whole endometrial tissue. 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.[98] High intrauterine levels of LNG lead to functional and histological changes within the endometrium, preventing implantation.[216-218] Sperm penetration is decreased due to changes in cervical mucus.[219] Most women (>75%) will continue to ovulate.[220;221] [EL=3]

Recommendation:
The main mechanism of action of the LNG-IUS as a contraceptive is to prevent implantation. Women should be advised that LNG-IUS as a contraceptive may act predominantly to prevent implantation and may not always prevent fertilisation. [GPP]

5.1.3 Use in the UK

In 2003/4, it is estimated that 1% of women aged 16-49 years in the UK 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 and TCu 380Ag users respectively at 4 years. No pregnancies were reported among users of either device at 5 years (1124 LNG-IUS users, 1121 TCu 380Ag users), 6 years (no data on number of women enrolled), and 7 years (897 LNG-IUS users, 896 TCu 380Ag users).[128][EL=1-]

LNG-IUS users from one RCT[137] 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.[222][EL=3]

LNG-IUS users from another RCT[139] were followed up in a non-comparative European study (n=109) reporting no pregnancies in LNG-IUS users in seven years of continuous use. 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.[223][EL=3]

Recommendation

LNG-IUS can be used as a long-term contraceptive and requires replacement every 7 years. [GPP]

5.1.5 The evidence

One systematic review[109] (n=19 RCTs and 11 cohort studies) was identified which assessed the effectiveness of 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.

5.2 Effectiveness

5.2.1 LNG-IUS

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.[224][EL=3]

5.2.2 LNG-IUS versus other contraceptive methods

(See 4.2.5)

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 in LNG-IUS and TCu 380Ag users respectively at 7 years.[128][EL=1-] Results of this RCT were included in 4 other reports during the 7-year study period.[129-133]

One RCT compared IUS-20 (n=141) and Nova T IUD (n=136) (formerly Novagard, copper surface 200) in Finland and Brazil and reported a pregnancy rate of 1/5495 women months and 7/5176 women months respectively at 5 years.[134][EL=1-] Results of this RCT were documented in 3 other reports during the 5-year study period.[135-137]

One European multicentre RCT compared IUS-20 (n=1821) and Nova T IUD

(n=937) (formerly Novagard, 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.[138;139][EL=1-] Results of this RCT were documented in two other reports during the 5-year study period.[140;141]

Interim results from the WHO international muticentred RCT (n=3815 insertions) showed a significant difference in cumulative pregnancy rates between LNG-IUS users (n=464) and TCu380A IUD users (n=580) at 6 years (0.5 versus 2.0).[127][EL=1-]

Summary of evidence

- **Unintended pregnancy rates with the LNG-IUS in situ have been reported between 0.5 and 1.1 per 100 women years at 5 years of use.**
- **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.**

Recommendations:
Women should be informed that there is a very small pregnancy rate (less than 5 women out of every 1000 users at the end of 5 years) associated with the use of LNG-IUS. [B]

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.[99][EL=4]

5.3.1 LNG-IUS

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.[224][EL=3]

5.3.2 IUS versus other contraceptive methods

(See 4.3.2)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu 380A 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).[128-132][EL=1-]

An RCT compared IUS-20 (n=141) and Nova T IUD (n=136)(copper surface 200) in Finland and Brazil. It reported cumulative continuation 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).[134-137][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 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.[138-141][EL=1-]

Interim results from the WHO international multicentred RCT (n=3815 insertions) reported no significant difference between LNG-IUS users (n=464) and TCu380A IUD users (n=580) in discontinuation rates due to expulsion (7.6% versus 8.3%) at 6 years.[127][EL=1-]

Summary of evidence

- **Expulsion rates of IUS are low: less than 10 in 100 over 5 years**

Recommendation:

Women should be advised that fewer than one in ten women will experience expulsion of LNG-IUS over a 5-year period. [C]

5.4 Discontinuation and reasons for discontinuation

(See 3.10)

5.4.1 LNG-IUS

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rate 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 oligo/amenorrhoea 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.[224][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). 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).[225][EL=3].

5.4.2 LNG-IUS versus other contraceptive methods

(See 4.4.3)

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 TCu 380Ag 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 difference 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 (1.0% versus 0.9% , 1.3% versus 1.5%, and 3.6% versus 3.6% at 1, 2 and 7 years respectively).[128-132][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.[134-137][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%, .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 due to depression between IUS and IUD (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.[138-141][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.[127][EL=1-]

Summary of evidence

- **Women request removals for a variety of reasons, which may vary in different cultures, as acceptability of anticipated side effects of the method differ. Discontinuation rates for all reasons, excluding and including expulsion and planned pregnancy at one year of use, range from 7 to 30%. (Table 5.1)**
- **Table 5.1 Cumulative discontinuation rates by reason:**

Reason for discontinuation		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Amenorrhoea 134;139 127;128	IUS	1.5 to 4.9 139 134 128 [EL=1+]	2.9 to 10.7 139 134 128 [EL=1+]	3.6 226 [EL=1+]	4.2 226 [EL=1+]	4.3 to 19.7 139 134 128 [EL=1+]	23.5 127 [EL=1+]	24.6 128 [EL=1+]

	IUD	0.0 to 0.1 [139] [134] [128] [EL=1+]	0.0 to 0.2 [139] [134] [128] [EL=1+]	0.0 [226] [EL=1+]	0.0 [226] [EL=1+]	0.0 to 0.4 [139] [134] [128] [EL=1+]	0.5 [127] [EL=1+]	1.1 [128] [EL=1+]
Other bleeding problems and pain [134;139] [127;128] [225]	IUS	6.0 to 7.4 [139] [134] [128] [EL=1+] 10.5 [225] [EL=3]	7.5 to 11.1 [139] [134] [128] [EL=1+] 12.6 [225] [EL=3]	13.0 [139] [EL=1+] 13.7 [225] [EL=3]	14.2 [139] [EL=1+] 14.7 [225] [EL=3]	11.0 to 15.4 [139] [134] [128] [EL=1+] 16.7 [225] [EL=3]	No data	20.4 [128] [EL=1+]
	IUD	3.5 to 7.3 [139] [134] [128] [EL=1+]	7.1 to 11.6 [139] [134] [128] [EL=1+]	15.3 [139] [EL=1+]	18.1 [139] [EL=1+]	20.4 to 23 [139] [134] [128] [EL=1+]	No data	30 [128] [EL=1+]
PID [134;139] [127;128] [225]	IUS	0.3 to 1.0 [139] [134] [128] [EL=1+]	0.5 to 1.3 [139] [134] [128] [EL=1+]	0.5 [139] [EL=1+] 1.2 [225] [EL=3]	0.5 [139] [EL=1+] 1.2 [225] [EL=3]	0.6 [139] [EL=1+] 1.2 [225] [EL=3]	0.3 [127] [EL=1+]	No data
	IUD	0.4 to 0.9 [139] [134] [EL=1+]	1.0 to 1.5 [139] [134] [EL=1+]	1.5 [139] [EL=1+]	1.5 [139] [EL=1+]	1.6 [139] [EL=1+]	0.1 [127] [EL=1+]	No data
Expulsion [134;139] [127;128] [225]	IUS	0.6 to 6.0 [139] [134] [128] [EL=1+] 4.5 [225] [EL=3]	0.6 to 7.3 [139] [134] [128] [EL=1+] 5.2 [225] [EL=3]	4.8 [139] [EL=1+] 5.5 [225] [EL=3]	4.9 [139] [EL=1+] 5.5 [225] [EL=3]	2.0 to 11.8 [139] [134] [128] [EL=1+] 5.9 [225] [EL=3]	7.6 [127] [EL=1+]	11.8 [128] [EL=1+]
	IUD	3.4 to 5.5 [139] [134] [128] [EL=1+]	4.1 to 6.1 [139] [134] [128] [EL=1+]	4.8 [139] [EL=1+]	5.3 [139] [EL=1+]	5.5 to 7.4 [139] [134] [128] [EL=1+]	8.3 [127] [EL=1+]	8.4 [128] [EL=1+]

- **Removal rates for hormone-related side effects excluding bleeding (such as headache, weight gain, acne, depression, PMS) range from 1.5 to 2.9%**
- **The rate of removals for PID ranges from 0.3 to 1.2%**

Recommendation:
Women should be advised that the most common side effects that lead to discontinuation of LNG-IUS use are:

- **bleeding problems**
- **pain**

The less common side effects are:

- **hormone-related**
- **pelvic inflammatory disease [B]**

5.5 Adverse effects

5.5.1. Bleeding problems

(See 4.5.1.2 and 5.4)

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 Cu T380A 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 age 30 or over using LNG-IUS were significantly less likely to complain of amenorrhoea, scanty bleeding and dysmenorrhoea than were younger women.[128][EL=1-] (Refer to 6.4)

Re-analyses of menstrual diaries (n=287) from one RCT[139] investigated

bleeding patterns in women with post-abortal and post-menstrual insertion of Nova-T IUD (formerly Novagard, 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.[146][EL=1-]

5.5.1.1 Management of bleeding problems

We did not identify any studies

Summary of evidence
(See 5.4)

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

5.6 Common symptoms and complaints

5.6.1 Weight change

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

5.6.1.1 LNG-IUS

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.[224][EL=3]

5.6.1.2 LNG-IUS versus other contraceptive methods

(See 4.6.1)

An European RCT reported that there is no evidence of a difference in body weight change among women using the copper releasing Nova-T (formerly Novagard, copper surface 200) (n=937) or the hormonal 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). Nonetheless, the removal of device due to weight gain was significantly different between LNG-IUS (1.5%) and IUD (0%).[139][EL=1+]

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported a statistically significant difference in the occurrence of weight gain (0.7% in the LNG-IUS group versus 0.4% in the IUD group).[128][EL=1-]

Summary of evidence

- **Whilst removals for weight gain were higher in LNG-IUS users than IUD users, there is conflicting evidence on whether the LNG-IUS is associated with no weight gain or a small level of weight gain.**

Recommendation:

Women should be informed that there is some evidence of body weight change in LNG-IUS users when compared with users of IUDs and that if it occurs, it is small and not a common reason for discontinuation. [C]

5.6.2 Altered mood and libido

The experience of sexual dysfunction such as loss of libido is common among young women. The incidence ranged from 5 to 30%.[153;154]

5.6.2.1 LNG-IUS

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.[224][EL=3]

5.6.2.2 LNG-IUS versus other contraceptive methods
(See 4.6.2)

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 CuT 380Ag IUD group). This study also reported no difference in the occurrence of depression (1.2% in the LNG-IUS group versus 1.1% in the CuT 380Ag IUD group).[128][EL=1-]

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

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.[227]

5.6.3.1 LNG-IUS

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.[224][EL=3]

5.6.3.2 LNG-IUS versus other contraceptive methods

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 CuT 380Ag IUD group).[128][EL=1-]

One European RCT comparing LNG-IUS with Nova-T IUD (likely to be formerly Novagard, copper surface 200, discontinued in 2001) reported a relative risk for acne of 5.56 (95% CI, 0.73 to 42.35) at the 5 year follow-up. In this study, acne was a reason for removal in 2.35% of IUS users versus 0.4% of IUD users.[139][EL=1+].

Summary of evidence

- **In a European RCT, there was a relative risk of developing acne of 5.56 compared with IUDs.**

Recommendation:
Women should be informed that they may be at an increased risk for developing acne, which may lead to requests for discontinuation of the LNG-IUS. [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.[228]

5.6.4.1 LNG-IUS

(See 5.4.1)

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.[224][EL=3]

5.6.4.2 LNG-IUS versus other contraceptive methods

(See 4.4.3 and 5.4.2)

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 CuT 380Ag IUD group) at 7 years.[128][EL=1-]

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.[49][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. [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.

(See 4.7.1)
In the cuurent 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.[49]

A small study identified transient bacteraemia from vaginal organisms in 13% of women within 10 minutes of IUD replacement/insertion.[158][EL=3]

In the current WHOMEC recommendations, LNG-IUS is assigned category '2' for women with history of deep vein thrombosis and pulmonary embolism and category '3' for women with current deep vein thrombosis and pulmonary embolism.[49][EL=1-4]

Recommendation:
Women with a history of venous thromboembolism (VTE) or who are at risk of VTE may use LNG-IUS, however an alternative method should be considered if VTE occurs during use. [GPP]

5.7.2 Bone mineral density

We did not identify any studies which addressed this question.

5.7.3 Ectopic pregnancy

(See 4.7.2)

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.[159] Ectopic pregnancy rate in women generally increases with age. However IUD failure rates decline with age.

5.7.3.1 LNG-IUS

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.[229][EL=3]

5.7.3.2 LNG-IUS versus other contraceptive methods

(See 4.7.2.2)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported 0 versus 2 ectopic pregnancies in LNG-IUS and CuT 380Ag users respectively at 7 years.[128][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.[139][EL=1-]

Interim results from the WHO international muticentred RCT (n=3815 insertions) reported a significant difference in ectopic pregnancy rate among LNG-IUS users (n=464) and TCu380A IUD users (n=580) at 6 years (0 versus 0.1).

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.[49][EL=4]

Summary of evidence

- **LNG-IUS prevents ectopic pregnancies. However, in the event of method failure the risk of an ectopic pregnancy is high.**
- **Ectopic pregnancy rates from 0 to 0.25% were reported in users of LNG-IUS.**

Recommendations:
Women should be advised that LNG-IUS prevents ectopic pregnancies. However, in the event of a method failure ectopic pregnancy should be excluded. [GPP]

Women with a history of previous ectopic pregnancy are at increased risk of future ectopic pregnancies. However, these women should be reassured that the risk of pregnancy, and therefore an ectopic pregnancy, while using the LNG-IUS is extremely low. [B]

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.[165-168] The role of actinomyces-like organisms in infection in IUD users is unclear.[169] They may be identified on cervical smears, but have not been shown to be predictive of any disease.[101;170-172]

IUDs users may have a higher risk of infection with actinomyces-like organisms compared to non-users.

(See 4.7.3.2)

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).[174][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.

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 TCu380Ag IUD groups.[128][EL=1-]

5.7.5 Pelvic inflammatory disease

(See 4.4, 4.7.4 and 5.4)

There is a possibility that infective organisms may be introduced during insertion of an IUD. The possible association between IUDs and Pelvic inflammatory disease (PID) has been an important concern about the device's safety and has influenced decisions on its use.

PID is associated with upper genital tract infection typically caused by Chlamydia trachomatis and Neisseria gonorrhoeae in the UK. In the majority of women, PID remains asymptomatic. When symptoms do appear, they often include fever, pelvic pain and vaginal discharge. Among women with PID, about 20% will become infertile and among those who conceive, about 10% of the pregnancies will be ectopic.[176]

The annual incidence of PID is estimated to be 1-2% in women of reproductive age in the US.[177] 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, regardless of types of IUD used. PID was significantly associated with the insertion of the IUD within the previous 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).[178][EL=1-]

5.7.5.1 LNG-IUS

(See 5.4.1)

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rate due to PID of0.9%, 1.2%, 1.2%, 1.2% and 1.2% at 1, 2, 3, 4 and 5 years respectively.[224][EL=3]

5.7.5.2 LNG-IUS versus other contraceptive methods

(See 4.7.4.2)

One multinational RCT (n=2246 women in Singapore, Brazil, Egypt and USA) reported no significant differences between LNG-IUS users and TCu 380A users in discontinuation rate due to PID (1.0% versus 0.9% , 1.3% versus 1.5%, and 3.6% versus 3.6% at 1, 2 and 7 years respectively).[128-132][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. [138-141][EL=1-]

A European RCT comparing LNG-IUS (n=1821) to Nova-T (n=937) (formerly Novagard, copper surface 200) reported a significant difference in cumulative discontinuation rates due to PID of 0·5 % versus 2·0% and 0·8% versus 2·2% respectively at 3 and 5 years.[138;139][EL=1+] (refer to IUS chapter)

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 6 years (0.3 versus 0.1).[127][EL=1-]

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.[49][EL=1-4] (Refer to IUD chapter)

Summary of evidence

- **The rate of PID was 0.7% in one study and 0.8% of women had removals of the LNG-IUS because of PID in another study.**
- **The risk of PID in users is low.**
- **Discontinuation of the method because of PID is lower (less than 1%) than among IUD users. Refer to IUD and PID post insertion here.**

Recommendation:
Women may be informed that the chance of developing PID following LNG-IUS insertion is very low at less than 1% over 1 year. [B]

5.7.6 Uterine perforation

Uterine perforation occurs in fewer than 1 in 1000 insertions.[99;182]

5.7.6.1 LNG-IUS

One UK non-comparative study (n=678) undertaken to determine the performance of LNG-IUS reported no perforation after 5 years of use.[224][EL=3]

The rate of perforation reported with LNG-IUS in an observational study was 0.9 per 1000 insertions.[230][EL=3]

5.7.6.2 LNG-IUS versus other contraceptive methods

(See 3.1 and 4.7.5.2)

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 TCu380Ag users at 7 years.[128][EL=1-]

Summary of evidence

- **The rate of perforation was found to be 0 to 0.1%**

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

5.8 Return to fertility

(See 3.1 and 4.8.2)

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.[141][EL=1-]

Another RCT reported a pregnancy rate of 96.4% in ex-LNG-IUS users (n=60) compared to 91.1% in ex-TCu 380Ag IUD users (n=50) at 1 year.[133;192][EL=1-]

A cohort study comparing pregnancy rates after cessation of use of LNG-IUS (n=91), TCu 380Ag (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.[231][EL=2]

Summary of evidence

- **Between 71% and 96% of women had achieved conception by 1 year after removal of LNG-IUS.**

Recommendation:
Women should be informed that return to fertility after removal of LNG-IUS is no different from that of users of the copper IUD, and appears to equate to the UK background fertility rate at 1 year. [B]

5.9 Details of method use

5.9.1 Assessment prior to fitting

(See 3.6)

All women considering the yse of LNG-IUS should be assessed as outlined for the IUD.[185] 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.

WHOMEC recommends that LNG-IUS should not be inserted when a woman has PID, or an STI, currently or within the last 3 months.[49] 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.[185]

Recommendations:
A healthcare worker fitting an 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. [GPP]

Women with identified risks associated with uterine or systemic

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

5.9.2 Position within the uterine cavity

(See 4.9.2)

5.9.3 Time of fitting of the LNG-IUS

5.9.3.1 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.[232]

5.9.3.2 When switching methods

The FFPRHC recommends that, when switching from another method of contraception, the LNG-IUS may be inserted at anytime if other hormonal methods have been used consistently and correctly.[233][EL=1+ to 4]

5.9.3.3 Following termination of pregnancy

WHOMEC recommends the LNG-IUS may be inserted immediately after surgical termination of pregnancy – first trimester or second trimester.[159] After medical termination of pregnancy, the insertion of the LNG-IUS should be performed at any time after the procedure is complete.[233]

5.9.3.4 Post delivery

Advice regarding postpartum insertion of the LNG-IUS follows that for the IUD.[185] The LNG-IUS may be inserted safely four or more weeks postpartum. The BNF recommends waiting until 6 weeks.[102]

5.10 Training of health professionals

(See 3.17)

5.11 Specific groups

5.11.1 Age

5.11.1.1 Adolescents

We did not identify any studies which assessed the use of LNG-IUS in adolescents.

LNG-IUS is assigned category '2' for women under 20 years.[49] 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.

5.11.2 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.[49]

5.11.3 Women who are breastfeeding

A cross sectional study (n=11) reported low concentrations of LNG in breast milk.[234][EL=3] It has been recommended that women who are breastfeeding, and who are four or more weeks postpartum may choose the LNG-IUS.[233]

LNG-IUS is assigned category '1' for women who are beyond four weeks postpartum and breastfeeding.[49]

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

5.12 Medical conditions and contraindications

5.12.1 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.[49]

5.12.2 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.[49]

Recommendation:
Emergency drugs including anticonvulsant medication should be available at the time of fitting a LNG-IUS in a woman known to be epileptic because there may be an increased risk of a fit at the time of cervical dilation. [GPP]

5.12.3 Sexually transmitted infections and HIV/AIDS

(See 3.11)

We did not identify any studies which addressed the use of LNG-IUS in women with HIV/AIDS. A local guideline for contraception for HIV positive women suggested that no increase in infection-related complications (PID) was noted in HIV positive women with intrauterine devices.[235][EL=4]

A systematic review 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.[236][EL=2-]

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.[49]

Summary of evidence

- **No evidence was identified of increased incidence of PID or increased rate of transmission of HIV to partners during use of LNG-IUS.**

03.03.05

Recommendation:
The LNG-IUS is a safe and effective method of contraception for women who are HIV positive or have AIDS. [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.[237][EL=3] LNG-IUS is assigned category '1' for women who are prescribed drugs which affect liver enzymes such as rifampicin and anti-convulsants.[49]

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.[238][EL=2-3] LNG-IUS is assigned category '1' for women who are prescribed anticonvulsants.[49].

5.13.1 Antibiotics

In the current WHOMEC recommendations, LNG-IUS is assigned category '1' for women who are prescribed antibiotics.[49]

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

5.14 Follow-up

(See 4.14)

We did not identify any studies. The UKSPR recommends a follow-up visit 3-6 weeks after insertion for IUD users.[64][EL=1-4]

5.14.1 Information prior to insertion

03.03.05

(See 3.5)

5.15 Economic evidence

The economic analysis carried out for the guideline demonstrated that the IUS dominates (i.e. it is both more effective and less costly) 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 £3,908 per additional pregnancy averted.

IUS also dominates the implant between 2 and up to 15 years of use examined. For one year of use, IUS is more costly and slightly more effective than the implant, with an Incremental Cost-Effectiveness Ratio (ICER) equalling £4,087 per pregnancy averted.

Compared to IUD, IUS is both less effective and more costly (dominated by IUD) for 2 and up to 4 years of use. For longer periods and up to the maximum 15-year time horizon examined, IUS becomes more effective than the IUD, but at an additional cost. The ICER of IUS compared to IUD decreases over time, starting from £18,583 per pregnancy averted for 5 years of use, and falling at £1,178 and £1,889 per pregnancy averted, compared to 5-year and 8-year licensed IUDs respectively, at 15 years of use. For one year of use, IUS is also more effective and more costly than IUD, with an ICER of £59,950 per pregnancy averted.

In summary, IUS is more cost-effective than the implant and the injectable starting from 2 years of contraceptive use and above. IUS is less cost-effective than IUD between 2 and 4 years of contraceptive use. Nevertheless, relative cost-effectiveness between IUS and other LARC methods is significantly affected by the level of discontinuation associated with LARC use.

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 was licensed in 1984 as a second-line contraceptive and in 1995 was given additional approval as a first-line contraceptive for long-term use. NET-EN is licensed for short-term use only.

Erosion of drug from the surface of the DMPA microcrystals provides a slow release and so 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.[239]

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.[240]

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 (lining of the uterus) make it an unfavourable environment for implantation.[241-244]

6.1.3 Use in the UK

It is estimated that fewer than 3% of women aged 16-49 in the UK chose injectables as their method of contraception in 2003/4.[1][EL=3]

6.1.4 Duration of action

DMPA is licensed for both short- and long-term use. In the UK, 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.

The ideal administration interval with NET-EN has been found to be 56 ± 7 days.[245] 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%.[241]

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.[246-248]

The time it takes for progestogen concentrations to be insufficient (i.e. to wear off) for contraception may vary from population to population.[249][EL=3]

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.

6.2 Effectiveness

POICs are highly effective contraceptive agents, with similar pregnancy rates to tubal occlusion, implants and the IUS.

6.2.1 DMPA versus NET-EN

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.[250][EL=1+] For DMPA, these effectiveness rates have been confirmed in one multinational RCT (0.7% at one year)[251][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.[252][EL=2+]

6.2.2 DMPA versus other contraceptive methods

(See 4.2.5)

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.[126][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.[253][EL=2-]

A cohort study in Nigeria was excluded because of poor quality.[254][EL=2]

Recommendation:
Women should be advised that POICs have very low pregnancy rates, no higher than 4 in 1000 at 2 years. DMPA (Depo medroxyprogesterone acetate) pregnancy rates are lower than NET-EN (Norethisterone enanthate). [C]

6.3 Discontinuation and reasons for discontinuation

(See 3.10)

The most common reason for discontinuation due to side effects is altered bleeding patterns. There are few direct comparisons of discontinuation of POICs and implants and none comparing POICs and Implanon.

6.3.1 DMPA

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.[255][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.[256-259][EL=3]

Two surveys conducted in Australia and New Zealand (n=247; n=252) reported discontinuation rates of 10% and 20% for bleeding disturbances among DMPA users.[260;261][EL=3]

6.3.2 NET-EN

A UK non-comparative study (n=707) reported cumulative discontinuation rate

of 23.4%, 36.3% and 66.2% at 1, 2 and 3 years among NET-EN users.[245][EL=3]

6.3.3 DMPA versus NET-EN

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).[250][EL=1+]

6.3.4 DMPA versus other contraceptive methods

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.[262][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.[263][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 (79% DMPA versus 44% OC).[253][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.[261][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%).[264][EL=3]

Recommendations:

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

Clinicians should know that as many as half of the women using DMPA discontinue by 1 year. [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

Bleeding patterns associated with POICs tend to be better tolerated by women than those associated with implants. This is because POICs, particularly DMPA, are more likely to induce amenorrhoea over time than implants, and amenorrhoea is generally more acceptable to women than prolonged or frequent bleeding. Amenorrhoea is a predictable side effect of DMPA and NET-EN, due to the inhibition of both ovulation and follicular development.

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 with the duration of POICs use. No significant differences in the incidence of 'bleeding problems' were reported among DMPA and NET-EN users at 1 and 2 years.[250][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.[255][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.[55][EL=3]

6.4.1.1 Management of bleeding problems

Amenorrhoea is common in women using DMPA. If unacceptable, an alternative method should be offered.[64][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.[265][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 groups in the duration or amount of bleeding.[266][EL=2-]

(See 3.5.3)

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.[55][EL=1+] [267][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.[54][EL=3]

Recommendation:
Women should be informed that amenorrhoea is a common side effect of POICs:

- **it is more likely with DMPA than NET-EN**
- **it is more likely as time goes by**
- **it is not harmful. [C]**

6.5 Common symptoms and complaints

6.5.1 Weight change

Weight increases with age in women of child-bearing age and the proportion of those categorised as overweight increases with each age decade.[need reference] Weight fluctuation in women of reproductive age is common, whether or not hormonal contraceptives are used. Many women are concerned that hormonal contraceptive use can lead to weight gain. Some studies show weight gain during POICs use and some show none. The mechanisms by which contraceptive hormones may affect body weight are not well known.

6.5.1.1 DMPA versus NET-EN

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.[250][EL=1+]

6.5.1.2 DMPA versus other contraceptive methods

A systematic review to update the WHOMEC guidance identified 2 studies. One study of adolescents reported 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 (n=239). The other study (n=885) reported similar weight gain (~2 kg) in DMPA users who weighed more or less than 91 kg at baseline.[268][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 and libido

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).[269][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.[270][EL=2-]
One US cohort study of adolescents (n=199) reported no differences in depression between users of DMPA and COC (53% versus 57%).[271][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.[272][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.[273] Progestogen only contraceptives, particularly the more androgenic progestogens such as LNG, tend to make the skin greasier and prone to acne.[227] 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).[264][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.[228] The prevalence of migraine has been estimated to be about 7% among adolescents.[274]

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.[271][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%).[264][EL=3]

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

6.6 Risks

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.

6.6.1 DMPA versus NET-EN

A cohort study (n=42) reported 15% versus 30% decreases in HDL cholesterol
from baseline with DMPA versus NET-EN at 1 year.[275][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.[276][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.[250][EL=1+]

6.6.2 DMPA versus other contraceptive methods

(See 4.7.1)
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 pressure between the two groups at 120 months.[156][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.[277][EL=2-]

Unlike the COC, DMPA is not associated with any increase in the risk of stroke, VTE or MI (Myocardial infarction). 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, venous thromboembolism, or acute myocardial infarction. 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), venous thromboembolism OR 2.19 (95% CI 0.66 to 7.26), and acute myocardial infarction OR 0.66 (95% CI 0.07 to 6.00).[92][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.[49]

DMPA is assigned category '4' for women with a blood pressure of over 160/110mmHg.[49]

Recommendation:
Clinicians should know that DMPA, and probably NET-EN, are safer than oestrogen-containing contraceptives for women who have arterial or venous risk factors. [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.[278][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).[279-281] 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 nonusers or users of other contraceptive methods, and others reporting no significant differences.

6.6.2.1 DMPA

The results from 8 cross-sectional studies that measured BMD in current DMPA users (age range 17 to 54 years) were used to derive Z scores.[282][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 nonusers, but all decreases were within 1 standard deviation of the mean of nonusers (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),[283-287] femoral neck,[283;284;286;287] ultradistal radius[279;281;288] was greater than at sites of predominantly cortical bone (midshaft ulna).[279;281;288][EL=3]

Among postmenopausal women who were past users of DMPA (n=34) compared with never 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).[289][EL=3]

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 nonusers.[290][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 nonusers (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.[286;291][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.[292][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.[293][EL=2-]

A cohort study assessed bone mineral density 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.[294][EL=2]

6.6.2.2 DMPA versus other contraceptive methods

Four cross-sectional studies reported BMD results in women who had used DMPA or a COC for at least 2 years.[279;280;295;296] Whilst one study reported that BMD at the distal radius was significantly lower in DMPA versus COC users (n=2474),[279] the other 3 studies did not report significant differences in BMD at the forearm, lumbar spine, or femur (n=60, 155, 189).[280;295;296][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.[297][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.[298][EL=2-] A 1-year US cohort study 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 (n=155).[299][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.[300][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.[288][EL=3]

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 nonusers.[290][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.[297][EL=2-]

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 symptoms of the menopause (n=32). T and Z scores were below the mean at both sites. Mean duration of DMPA use was 52 months.[301][EL=3]

6.6.2.3 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%).[302][EL=1+]

The Department of Health has issued an alert on the use of DMPA.[303]
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.
Guidance from FFPRHC on the use of DMPA in relation to BMD is available.[304]

Recommendations:
All women should be advised that the use of DMPA is associated with a small loss of bone mineral density perhaps not all of which is recovered when the method is stopped. [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 be appropriately informed and supported in their choice. [GPP]

6.6.2.4 Osteoporosis

We did not identify any studies

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 POICs 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.[49][EL=4]

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

6.7 Return to fertility

POICs are the only progestogen only methods to cause a delay in the return of fertility. The delay for DMPA is greater than for NET-EN.

6.7.1 DMPA

Another seven non-comparative studies reported that ovulation occurred between 3 to 6 months after DMPA injection. [305;305-310][EL=3]

6.7.2 DMPA versus NET-EN

One cohort study (n=24) reported significant differences in time to return of ovulation among DMPA and NET-EN users 90 days after their last injection (5.5 versus 2.6 months).[311][EL=2-]

6.7.3 DMPA versus other contraceptive methods

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).[312][EL=2-]

A systematic review of one 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).[313][EL=2+]

Recommendations:
Women should be told that there is likely to be a delay of up to 1 year in the return of fertility after discontinuation of POICs [C]

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

6.8 Details of method use

6.8.1 Assessment prior to initiation

(See 3.6)

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.

Massaging at the site of the progestogen only injection should be avoided as this increases immediate absorption.

6.8.3 Time of first Injection

The UK Selected Practice Recommendations (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. The woman will need to abstain from sex or additional contraceptive protection should be used for the first seven days after injection.[64][EL=4]

Recommendation:

POICs may be started up to and including the fifth day of the menstrual cycle. No additional contraceptive protection is needed. POICs 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. [GPP]

6.8.3.1 Management of delayed injections

(See 6.7)

For delayed injections, the UKSPR recommended that repeat injections may be given up to 2 weeks late without additional contraceptive protection.[64][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.[314]

Recommendations:

Repeat injections of DMPA should be given every 12 weeks and for Noristerat every 8 weeks. [B]

Women attending up to 2 weeks late may be given either injection if it is reasonably sure that they are not pregnant. [GPP]

6.8.3.2 Post-abortion

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.[315][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).[246][EL=4]

DMPA and NET-EN are assigned category '1' for women immediately post-abortion in the current WHOMEC recommendations.[49][EL=1-4]

Recommendation:
DMPA and NET-EN may be given immediately following abortion (spontaneous or induced). [GPP]

6.9 Training of health professionals

(See 3.17)

6.10 Specific groups

6.10.1 Age

6.10.1.1 Adolescents

(See 6.6.2)

6.10.1.2 Women aged over 35 years

Women over 35 have a minimal increase in the risk of CVD if they do not smoke, and have no other risk factors, such as hypertension or diabetes.[241][EL=2-] In the current WHOMEC, POICs are assigned category '3' for women with multiple arterial risk factors such as smoking, diabetes and hypertension.[49]

The use of POICs by women older than 40 years needs caution.[316][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.

Recommendation:
Caution should be used in recommending DMPA to adolescents and women aged over 35 but in general the benefits outweigh the risks. [GPP]

6.10.2 Women with body mass index over 30

We did no 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.[49;268][EL=2++]

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

6.10.3 Women who are breastfeeding

Concern has been expressed that progestogens may affect breast milk constituents and ,as a result, 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 progestogen only contraceptives (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.[317][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.[318][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.[319][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.[49][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.[64]

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.[49][EL=1-4]

Recommendation:
Breastfeeding women may be advised that they can use POICs before the sixth week after childbirth if other methods are unacceptable. [C]

6.11 Medical conditions and contraindications

6.11.1 Diabetes

We did not identify any studies.

6.11.2 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.[320][EL=3]

DMPA and NET-EN are assigned category '1' for women with epilepsy in the current WHOMEC recommendations.[49][EL=1-4]

Recommendation:
In women with epilepsy requiring contraception the use of DMPA may be associated with a reduction in the frequency of seizures. [GPP]

6.11.3 Sexually transmitted infections and HIV/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.[49;203][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.[321-323] A meta-analysis reported a significant association between oral contraceptive use and HIV-1 seroprevalence.[324]

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).[325;326][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.[49;203][EL=1-4]

Recommendation:
There is no evidence to suggest a causal relationship between the use of DMPA and an increased risk of STI (sexually transmitted infections) or HIV acquisition. Women at increased risk of STI including HIV 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 POICs is recommended. [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 POICs in those taking liver enzyme-inducing medication or to reduce the injection interval. [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).[327][EL=1+]

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.

6.14 Economic evidence

According to the results of economic evaluation of LARC methods undertaken for this guideline, 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 between 2-15 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 IUD, the implant and the IUS compared to the injectable for one year of use are £16, £3,905 and £3,908 per pregnancy averted respectively.

In summary, the injectable is less cost-effective than all other LARC methods between 2 and 15 years of contraceptive use. It should be noted, though, that

relative cost-effectiveness between the injectable and other LARC methods is highly sensitive to changes in their discontinuation rates.

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 60 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.[328;329]

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.[328] 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.[330;331]

7.1.3 Use in the UK

It is estimated that fewer than 3% of women aged 16-49 in the UK 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.

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.[109] 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. 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.

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). These clinical trials (a total of 8 RCTs and 12 non-comparative studies) have been reviewed by one systematic review[109] and a series of meta-analyses[332-337]. Individual trials from the same series have also been published by different authors.[40;338-342]

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. Revised analysis, including data from new trials, will be available in late 2004. No such analysis has been received from this pharmaceutical company to date.

However, 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, provided it is inserted in the appropriate manner according to the product information.'[343] Evidence which compared Implanon with Norplant presented in this chapter is based on original published data from these clinical trials before the Indonesian trials were withdrawn, and should therefore be interpreted with caution. 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

7.2.1 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.[333*332*][EL=1-] These clinical trials were conducted by a pharmaceutical company.

A systematic review (n= 7 RCTs; 1628 women; 43001 woman months of follow-up) reported no pregnancies at 4 years among women using Implanon or Norplant.[109*][EL = 1-] The RCTs reviewed were part of the multinational clinical trials conducted by a pharmaceutical company.[332*]

7.2.2 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)(a combination of TCu 220C, TCu 380A, Multiload 250 and 375 or Shanghai V) and sterilisation

(n=1419). Five-year follow-up was completed by 94.6% of the women enrolled. The cumulative pregnancy rates for Norplant, copper IUDs and tubal occlusion were 0.12, 1.02, 0.21 and 0.53, 3.04, 0.5 respectively at 1 and 3 years.[163;344][EL=2+]

A 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 pregnancy in either group at 1 year.[345][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.[41][EL=2+]

The GDG considered this evidence, but 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 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.)

Summary of Evidence

- **No pregnancies were reported in women using Implanon.**
- **The GDG were aware of reports of pregnancies using Implanon.**

Recommendation:

Women should be advised that subdermal implants have very low pregnancy rates (less than 1 in 1000). [B]

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, however, a woman does need to visit a health service facility. In the UK, a relatively small number of clinicians have been trained to remove implants. The geographical inconvenience of attending a particular clinic for implant removal may encourage women to postpone removal for longer.[346] 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.

7.3.1 Implanon versus Norplant

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.[333*336*332*][EL=1- to 3]

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.

7.3.2 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.[163;344][EL=2+]

A cohort study (n=755) compared discontinuation rates between Norplant and IUDs (copper content not reported) 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 reasons 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.[346][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.[41][EL=2+]

Interim data from an unpublished study in Edinburgh (n=331 Implanon insertions; data completed on 262 women) reported a removal rate of 13% within 6 months, 27% at 1 year, 44% at 2 years and 57% at 3 years 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) [347][EL=3]

Summary of Evidence

- **The commonest reason for discontinuation of contraceptive implants is bleeding disturbances.**
- **Almost one third of women will have had 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 one third of women will discontinue Implanon within 2 years because of irregular bleeding. Less than 1 in 10 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 events effect among healthy Implanon users.[348][EL=1-3] Implanon and Norplant are assigned a category '1' rating for healthy women from menarche to before the menopause (18 to >40).[49][EL=1-4]

A meta-analysis of clinical trials reported no death in any of the clinical development trials of Implanon.[332*][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.[94;163][EL=2+] None of these deaths was considered to be a direct consequence of the contraceptive implant.

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.[349] 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.[350]

7.4.1.1 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.[332*][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.[336*333*][EL=1-]

7.4.1.2 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. [271][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 (formerly Novagard, copper surface 200). 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).[345][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 sterilized 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).[163;344][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).[163][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 irregular 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]

7.4.1.3 Management of bleeding problems

We did not identify any studies which assessed the management of bleeding problems in Implanon users.

A RCT (n=67) 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 than in the placebo group (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.[351][EL=1+]

One RCT (n=150) 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 than in the ethinylestradiol group and in the placebo group (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.[352][EL=1+]

Preliminary results from another RCT (n=48) reported a significant reduction in the mean number of bleeding days at 3 months in Norplant users treated with either ethinylestradiol or the combined pill when compared with placebo (19.2 ± 3.4 versus 18.2 ± 1.9 versus 28.6 ± 5.4).[353][EL=1+]

Preliminary results from a RCT (n=72) reported a significant reduction in the mean number of bleeding days in Norplant users treated with vitamin E supplementation when compared with placebo (7.7 ± 1.4 days versus 12.1 ± 1.3 days).[354][EL=1+]

A RCT (n= 64) reported no significant difference in clinical improvement of bleeding problems in Norplant users with transdermal estradiol patch when compared with placebo patch (70% versus 42%).[355][EL=1+]

A multicentre RCT (n= 486) (In press) compared vitamin E, aspirin, vitamin E and aspirin, and placebo 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.[356][EL=1-]

Summary of evidence

- **There is some evidence to support a beneficial effect of mefenamic acid or ethinylestradiol, alone or as an OCP, 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:
Clinicians should be advised that non-hormonal treatment with mefenamic acid or hormonal treatment with ethinylestradiol is moderately effective in stopping irregular bleeding during implant use. [B]

7.5 Common symptoms and complaints

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.

7.5.1.1 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.[332*][EL=1-]

7.5.1.2 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.[94][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.[271][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.[345][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;**
- **Any change in weight is small.**

Recommendation:
Women should be informed that the use of Implanon is not associated with a significant change in weight. [C]

7.5.2 Altered mood

We did not identify any studies which assessed the effect of Implanon on mood changes.

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).[94][EL=2+]

These results may not be extrapolated to Implanon since the type of progestogen and effect on bleeding patterns are different.

Summary of evidence

- **There is no evidence for a causal link between the use of implants and mood change.**
- **There is limited evidence for altered mood in a small number of Norplant users. It may not be appropriate to extrapolate this to Implanon.**

Recommendation:
Women should be informed that the use of Implanon is not associated with significant adverse mood changes. [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%.[153;154]

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.[332*][EL=1-]

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.[273] 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.[227] In contrast, the combined oral contraceptive is beneficial for acne so women who change from a combined method to progestogen only method may notice an increase in acne.

7.4.1 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.[332*][EL=1-]

7.4.2 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).[94][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.[271][EL=2-]

Summary of evidence

- **One study suggested that Norplant increases the incidence of acne.**

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.[228] The prevalence of migraine is estimated to be about 7% among adolescents.[274]

7.5.5.1 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.[332*][EL=1-]

7.5.5.2 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).[94][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.[271][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 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 venous thromboembolism. Concern has also been raised regarding coronary artery disease and the association of metabolic alterations caused by hormonal contraceptives. Progestogen only contraceptives do not appear to be associated with an increased risk of cardiovascular disease.

7.6.1.1 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.[357][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.[332;335*][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.[358][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.[359][EL=1-]

One RCT (n=80) reported no significant changes in serum lipid ratios among Implanon and Norplant users at 2 years.[360][EL=1-]

Alterations in glucose and insulin levels may be related to the risk of cardiovascular disease.[361] 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.[362][EL=1-]

7.6.1.2 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.[94][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.[271][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 progestogen only contraceptives 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.[363] There is an association between the suppressive effect of progestogen on ovarian oestrogen secretion and bone loss.[364] The evidence to date on whether or not subdermal implants cause a reduction in BMD is inconclusive.

7.6.2.1 Implanon

A systematic review to update the current WHOMEC recommendations reported no evidence of an adverse effect on bone mineral density among healthy Implanon users.[348][EL=1-3]

7.6.2.2 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 bone mineral density 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.[365][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.[160] 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.[94][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.[366][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.[46][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.[49][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 reassured that there is no evidence for a teratogenic effect of Implanon. Nevertheless, should pregnancy occur and be continued, the implant should be removed. [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.

7.7.1 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.[332*][EL=1-].

7.7.2 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.[313][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.[367][EL=2-]

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:
The use of contraceptive implants does not impair fertility on discontinuation. [C]

7.8 Details of method use

7.8.1 Assessment prior to insertion

(See 3.6)

7.8.2 Time of insertion of implants

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.[368;369][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.[370][EL=1-]

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.[371]

7.8.3 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 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.[337][EL=1-]

Implanon was associated with a significantly lower frequency of removal complications when compared with Norplant (0.2% versus 4.8%).[332*337*372*][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.[333*][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:

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

7.9 Training of health professionals

(See 3.17)

7.10 Specific groups

7.10.1 Age

7.10.1 Young people/adolescents

We did not identify any studies which assessed the use of Implanon among adolescents

7.10.1.1 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.[373][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.[374][EL=2-]

7.10.1.2 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.[375][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 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%).[376][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.[271][EL=2-] (see also under Menstrual Disturbances 8.4.1)

A cohort study (n=48) of adolescents (12 to 21 years) reported no significant differences in bone mineral density 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).[298][EL=2-] (See also under Bone Mineral Density in 8.7.2)

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.[377][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 high level of interest in Norplant.[378][EL=3]

Norplant is assigned category '1' for women aged under 18 in the current WHOMEC recommendations.[159][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 in 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. [C]

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

7.10.2 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).[332*] [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.[49] [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 reassured that, as potential users of Implanon, there is no evidence for a higher rate of pregnancy among women weighing over 70kg. [GPP]

7.10.3 Women who are breastfeeding

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) (copper dose not reported) at 6 weeks postpartum. There were no significant changes between the 2 groups in milk content of fat, protein and lactose.[379][EL= 2-]

A cohort study (n=108) reported that initiation of Norplant in healthy lactating women around day 60 postpartum 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.[380][EL=2+]

Beyond six weeks post partum, Implanon is assigned category '1'. Up to six weeks post partum WHOMEC considers Implanon a category '3'.[49] 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.**

03.03.05

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. [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.

7.11.1 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.[213][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.[381][EL=3]

Norplant and Implanon are assigned category '1' rating for women with history of gestational disease, '2' rating for women with insulin and non-insulin dependent diabetes in the current WHOMEC recommendations.[49][EL=2-]

Summary of evidence

- **There was no evidence of significant disturbance to diabetic control in women using Norplant.**

Recommendation:
Implanon is not contraindicated for women with diabetes. [C]

7.11.2 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.[382;383][EL=2-]

7.11.3 Sexually transmitted infections and HIV/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.[236][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.[159][EL=2-]

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)

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.[382;383][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.[49][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. [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.[64][EL=1-4]

Recommendation:
No routine followup after implant insertion is required. [GPP]

7.14 Economic evidence

The economic analysis conducted for this guideline showed that the implant is dominated (i.e. it is less effective and more costly) by the IUD for contraceptive use equal to 2 years and up to 15 years, which was the longest period of contraceptive use examined. For one year of use, the implant is more effective and more expensive than IUD, demonstrating an Incremental Cost-Effectiveness Ratio (ICER) of £82,095 per pregnancy averted.

The implant is also dominated by the IUS between 2 and 15 years of contraceptive use. For one year of use, IUS is more costly and slightly more effective than the implant, with an ICER equal to £4,087 per pregnancy averted.

Compared to the injectable, the implant is the dominant option (more effective, less costly) for 2-15 years of use. For one year of use the implant is more effective than the injectable, at an additional cost of £3,905 per pregnancy averted.

In conclusion, the implant is less cost-effective than IUD and IUS between 2 and 15 years of use, but it is more cost-effective than the injectable over the same time period examined. Its relative cost-effectiveness to other LARC

methods is determined by the level of discontinuation associated with LARC use.

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

8 Economic evaluation

8.1 Introduction

The aim of the economic evaluation was to estimate the relative cost-effectiveness of long-acting reversible contraceptive methods (LARC methods) in comparison to the male condom, the combined oral contraceptive pill (COC), and also non-reversible contraceptive methods, i.e. vasectomy and female sterilisation, in the UK. 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 1082. All paper abstracts were reviewed, and 23 articles were retrieved and critically appraised. Thirteen 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[384-391] and one in Thailand.[392] The general conclusion drawn by these studies was that all contraceptive methods provided substantial cost-savings compared to no method.[384-388] Female and male sterilisation were shown to be the most cost-effective methods (highest level of effectiveness at lowest cost) in the long term.[387;389;390] LARC methods were also highly cost-effective, especially IUDs and the IUS, followed by the injectable and the implant.[387-390] Two studies that assessed the cost-effectiveness of the implant showed that it depended highly on the duration of use of the method.[391;392] 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 to the UK context.

Four studies (one of which was an update of an earlier study using the same methods) were conducted in the UK, published from 1995 to 2000.[109;393-395] 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 four 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 study was considered as 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
Phillips 2000 [393]	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 not included.	*Pregnancies averted compared to no method*	Net savings per patient Additional cost per pregnancy averted in comparison to DMPA and COC.	Comparisons were made between each method and no method. Direct comparison was made only between Implanon and DMPA, and also mplanon and COC.
McGuire and Hughes, 1995 [394] Hughes and McGuire, 1996 (updated study) [395]	Contraceptive methods available in the UK: OC, diaphragm, IUD, condom, injectable, spermicide, implant, vasectomy, sterilization.	NHS viewpoint, 1991 prices. Included: *Method costs* *Savings due to pregnancies averted* (compared to no method) Excluded: Costs associated with side effects & discontinuations.	*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 [109]	Norplant compared with: IUD>250mm^3, IUD≤250mm^3, OC, DMPA. Mirena compared with: IUD>250mm^3, IUD≤250mm^3.	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.	*Pregnancies averted*	*Incremental cost-effectiveness ratio: Additional costs per additional pregnancy averted.*	Effectiveness rates based on a systematic review and meta-analysis. 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) and costs to the health service associated with outcomes of unintended pregnancies, i.e. live births, miscarriages and abortions. In some studies 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. Adverse events and secondary beneficial effects of contraception were also not considered in the studies.

With the exception of one study[393] the additional costs associated with 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 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[393-395] or with another contraceptive method.[109]

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[394] and their updated study[395],

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,[393] 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[109] 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).[393]

8.2.4 Overall findings from the UK-based literature

McGuire and Hughes[394;395] 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[109] 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 Philips study,[393] commissioned by the manufacturers of Implanon, demonstrated that LARC methods provided effective contraceptive protection and represented value for money from the perspective of the health care service. 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 and additional method cost of £616 per additional pregnancy averted (in this case costs associated with 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[393] and adverse effects. 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 management of side effects of contraceptive use were also not considered in 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, since this issue was not related to the scope of the guideline.

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 this 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 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. Therefore, the relative cost-effectiveness between contraceptive methods was determined not only by effectiveness rates, but also by the rates of discontinuation associated with each method.

Finally, an update of cost and effectiveness data was considered essential, since 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[396] and the protective role of male condom against sexually transmitted diseases) were not considered in the estimation of costs, as relevant data were difficult to identify, since 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 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 guideline or 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.[397-400] 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).[384;385;387] However, the GDG expressed the opinion 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;401] Where failure rates were not reported in the guideline, these were derived from a published review.[402] 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 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 rest 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 be considering 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.

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 used). Two analyses, assuming 5 and 8 years duration of use of an IUD device, were undertaken. This was decided because, although T-Safe is licensed for 8 years, other IUDs have a 5-years licensed duration, and this should be reflected in the results.
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.[403]

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 2003 NHS reference costs,[404] due to lack of research-based data. Ingredient costs were derived from the British National Formulary, March 2005.[102] 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 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[405] due to 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 were derived from published literature.[406]

Ingredient costs and unit costs of GP consultations used in the model are presented in Table 8.2.

Table 8.3 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). 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 rest outcomes of unintended pregnancy was based on national statistics,[407;408] a literature review on unintended pregnancy[396-399] 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.[402;409-412] All effectiveness data and other clinical input parameters included in the analysis are presented in Table 8.4.

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.[413]

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 not tested in a sensitivity analysis, as the GDG could not identify ranges of values for this purpose. Only a rough illustration of the impact of discontinuation on the base-case results was attempted, by assuming elimination of discontinuation, where relevant, at 1%. Alternative input values and hypotheses tested in sensitivity analyses are reported in the respective sections of the results.

Table 8.2 Ingredient costs of contraceptive methods – GP unit costs

Contraceptive method	Ingredient cost[102]	Licensed duration of use[102]
IUD: T-Safe CU 380A	£09.56 per device	8 years
POIUS	£83.16 per device	5 years
POICs: DMPA	£05.01 per dose	N/A
POSDIs	£90.00 per device	3 years
Male condom	£00.56 per item (retail price)	N/A
COC (weighted, average [403])	£01.37 per month	N/A
General Practitioner unit cost [406]	£2.24 per surgery/clinic minute, including direct care staff costs and qualification costs	

Table 8.3 Cost data included in the model

Procedure or event	Baseline value	Comments
IUD method cost First year cost: Total 5 or 8 year cost:	 £133 £158	Resource use consisting of an initial 20 min GP consultation, an 18 min consultation for insertion, a 9 min follow-up routine consultation 3-6 weeks after insertion, and a 10 min consultation for removal; GDG consensus.
POIUS method cost First year cost: Total 5 year cost:	 £207 £232	Resource use consisting of an initial 20 min GP consultation, an 18 min consultation for insertion, a 9 min follow-up routine consultation 3-6 weeks after insertion, and a 10 min consultation for removal; GDG consensus
POICs method cost Annual method cost • First year: • Following years: 3 year cost: 5 year cost: 8 year cost:	 £144 £99 £342 £540 £837	Resource use consisting of an initial 20 min GP consultation (included only in the first year of use), and an 8 min consultation for injection every 12 weeks; GDG consensus.
POSDIs method cost First year cost: Total 3 year cost:	 £175 £230	Resource use consisting of an initial 20 min GP consultation, a 16 min consultation for insertion and a 22 min consultation for removal; GDG consensus.
Male condom method cost Annual method cost: 3 year cost: 5 year cost: 8 year cost:	 £29.00 £87.00 £145.00 £232.00	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.[414]
COC - method cost Annual method cost • First year: • Following years: 3 year cost: 5 year cost: 8 year cost:	 £106 £61 £228 £350 £533	Resource use consisting of an initial 20 min GP consultation (included only in the first year of use), and 2 GP routine consultations per year, lasting 10 min each; GDG consensus.
Female sterilisation	£683	Weighted average NHS reference cost 2003 for Upper Genital Tract Intermediate Procedures (elective, non-elective and day-cases)[404], adding an initial 20 min GP consultation cost. In case of contraceptive failure, repeat of the procedure was considered.
Vasectomy	£433	It was estimated that 2/3 of vasectomies take place in GP practices and 1/3 in hospitals/community care settings.[401] 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 2003 (elective, non-elective, day-cases and community-based services) was used[61] 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.[401] 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:	£2147	NHS reference cost 2003, including cost of antenatal care, live birth, care of unhealthy neonates and neonate ICU levels 1 & 2.[404]
Cost of antenatal care:	£476	Costs of antenatal clinics, outpatient obstetrics and community midwifery visits were attached to the total number of births reported in the document.
Cost of live birth:	£1197	Weighted average of normal deliveries, assisted deliveries, and

Total cost of live birth: (including care of unhealthy neonates + ICU for unstable neonates)	£1671	caesarean sections, treated as elective, non-elective, and day cases or in community services. Costs of neonates that died within 2 days of birth or had one/multiple minor/major diagnoses were attached to the total number of births reported in the document. Costs of neonatal intensive care levels 1 & 2 were also attached to the number of births.
Abortion	£425	Weighted average NHS reference cost 2003 (surgical or medical termination of pregnancy, treated as elective, non-elective or day case, or in outpatient gynaecology clinic).[404]
Miscarriage	£299	Weighted average NHS reference cost 2003 (elective, non-elective and day-cases)[404] and GP fee for miscarriage 2004 (£77.50).[405] It was assumed that 30% of miscarriages were treated by GPs (GDG expert opinion).
Ectopic pregnancy	£1,213	Weighted average NHS reference cost 2003 (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).[404] The relative weights used for the estimation of costs were based on Scottish data.[415] 58% of ectopic pregnancy management involves laparoscopy, 35% involves laparotomy, and 7% of ectopic pregnancies are medically managed.

Table 8.4 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%	
POIUS		
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%	
POICs		
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%	
POSDIs		
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.[402]
COC		
Years 1-15:	8%	Failure rate for typical use, based on a published review.[402]
Female sterilisation		
Year 0-1:	0.500%	The failure rate for the first year was based on a published review.[402] 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[409] 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.[402] The annual failure rate used for the following years is that reported in the RCOG guideline on sterilisation after clearance has been given.[409]
Years 1-15:	0.050%	
Average contr. 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 based on data reported in the guideline and 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.
POIUS 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 POIUS use were based on data reported in the guideline and 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.
POICs Year 0-1: Year 1-2: Following years:	 55.5% 5.5% 5%*	Discontinuation rates for the first 2 years of POICs use were based on data reported in the guideline and 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.
POSDIs Year 0-1: Year 1-2: Year 2-3: Year 3-4 (reinsertion): Following years:	 27.1% 17.1% 13.0% 8.8% 1%*	Discontinuation rates for the first 4 years of POSDIs use (including re-insertion) were based on data reported in the guideline and 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 probability of ectopic pregnancy	Baseline value	Comments
IUD:	6%	Based on data reported in the guideline.
POIUS:	25%	Based on data reported in the guideline.
POICs:	1.15%	For POICs, POSDIs, male condom, COC, vasectomy and average contraceptive method, the incidence of ectopic pregnancy among pregnancies in the general population in the UK was used.[410]
POSDIs:	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[411] and consistent with the range of values reported in the RCOG guideline on sterilisation[409] and a published review.[412]
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)		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)[407]. 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.[408] 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.[394;397-399] Consequently, abortions account for 40.6% (20.3% x 2) of *unintended* pregnancies, which is in agreement with the findings of published studies.[398;400] The remaining 46.4% of *unintended* pregnancies represents live births.
Live birth:	46.4%	
Abortion:	40.6%	
Miscarriage:	13%	
Discount rate	3.5%	Recommended by NICE guidance on Health Technology Appraisal, [102] 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 that that of the comparator.

Results are presented in separate sections for each of the main comparisons performed:

1. comparisons of LARC methods with male condom
2. comparisons of LARC methods with COC
3. comparisons of LARC methods with female and male sterilization
4. comparisons across LARC methods

In each section, full 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 with the exception of those of the scenario involving combination of LARC methods with male condom, as it was considered that such a pattern of contraceptive use may be relevant to a significantly big group of women seeking contraception, as, besides contraceptive protection, it also protects against sexually transmitted infections (STIs).

Results are reported for a time frame ranging from one and up to fifteen years of contraceptive use.

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 could be drawn, as no threshold value for the ICER that would allow for such a conclusion could be identified.

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 explained 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 increases reaching the full licensed duration of use of each LARC device, as 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 all forms of contraception examined are in general 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 Comparison of LARC methods with male condom

8.4.1.1 Base-case analysis

The IUD and the injectable dominate the male condom (they are more effective and less costly) constantly, for all time frames examined, starting from one and up to 15 years of use. The IUS and the implant are more effective and more costly than the male condom for one year of contraceptive use, incurring additional costs equal to £461 and £452 per additional pregnancy averted, respectively. After one year of use, both of these methods dominate the male condom as well. Results for one and up to 4 years of use are shown in table 8.5. Results for longer periods of use, demonstrating the persisting dominance of LARC methods versus the male condom over time, are not presented.

Table 8.5 Total costs and pregnancies per 1000 women: LARC versus male condom

1 year of use	Total pregnancies	Total costs	Incremental Cost-Effectiveness Ratio LARC method versus condom
Condom	150	208,269	
IUD	18	194,766	LARC dominates
IUS	17	269,610	£461 per additional pregnancy averted
Injectable	36	194,477	LARC dominates
Implant	17	268,162	£452 per additional pregnancy averted

2 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus condom
Condom	295	409,495	
IUD	55	254,746	LARC dominates
IUS	57	334,447	LARC dominates
Injectable	110	345,477	LARC dominates
Implant	62	339,990	LARC dominates

3 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus condom
Condom	435	603,916	
IUD	105	333,845	LARC dominates
IUS	109	414,251	LARC dominates
Injectable	184	492,116	LARC dominates
Implant	122	434,729	LARC dominates

4 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus condom
Condom	570	791,762	
IUD	166	426,841	LARC dominates
IUS	167	502,658	LARC dominates
Injectable	258	635,307	LARC dominates
Implant	193	617,484	LARC dominates

Evidence statement:

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

8.4.1.2 Sensitivity analysis

8.4.1.2.1 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 condom users are likely to make the choice of condom not only as a contraceptive method, but also as a method of protection against STIs. Therefore, 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 consequently 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.

Results show that LARC methods combined with male condom are more effective and more costly than the male condom alone for one year of contraceptive use, incurring additional costs ranging from £61 (injectable) to £651 (IUS) per additional pregnancy averted. 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. Results for one and up to 4 years of use are shown in table 8.6. Results for longer periods of use, showing the persisting dominance of combinations of LARC methods with male condom compared to the male condom alone over time, are not presented.

Table 8.6 Total costs and pregnancies per 1000 women: Combination of LARC plus male condom versus male condom alone

1 year of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method plus condom versus condom alone
Condom	150	208,269	
IUD	18	220,500	£93 per additional pregnancy averted
IUS	17	294,859	£651 per additional pregnancy averted
Injectable	36	215,199	£61 per additional pregnancy averted
Implant	17	293,123	£640 per additional pregnancy averted

2 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method plus condom versus condom alone
Condom	295	409,495	
IUD	55	300,500	LARC dominates
IUS	57	378,736	LARC dominates
Injectable	110	377,861	LARC dominates
Implant	62	382,915	LARC dominates

3 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method plus condom versus condom alone
Condom	435	603,916	
IUD	105	395,541	LARC dominates
IUS	109	474,022	LARC dominates
Injectable	184	534,782	LARC dominates
Implant	122	490,951	LARC dominates

4 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method plus condom versus condom alone
Condom	570	791,762	
IUD	166	501,224	LARC dominates
IUS	167	575,518	LARC dominates
Injectable	258	687,411	LARC dominates
Implant	193	683,718	LARC dominates

Evidence statement:
LARC methods combined with male condom are most cost-effective compared to male condom alone for 2 of use and above; for one year of use they are more effective, at an additional cost ranging from £61 (injectable) to £651 (IUS) per additional pregnancy averted.

8.4.1.2.2 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 and the injectable alone become slightly more costly than male condom for one year of use (ICERs approximately £35 per pregnancy averted for both methods), whereas the rest ICERs (of LARC alone or combined to male condom versus male condom alone) remain at the same levels. All LARC methods (alone or combined with condom) become the dominant options after one year of use and above. Increasing the number of condoms used per year or the ingredient cost would only favour LARC methods even more.

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.

8.4.1.2.3 Variability in effectiveness rates of LARC methods

No sensitivity analysis was undertaken to examine the impact of uncertainty in the failure rates of LARC methods used in the economic analysis, as no ranges of values appropriate for this purpose could be identified. However, small (as expected) changes in failure rates, compared with the comparatively

very high failure rate of male condom, are not considered to have any impact on the base-case results.

8.4.1.2.4 Variability in discontinuation rates of LARC methods

Decreasing discontinuation rates of LARC methods would favour their relative cost-effectiveness versus male condom. An increase in LARC discontinuation rates was not considered, since the rates reported were thought to be already relatively high.

8.4.1.2.5 Perfect use of male condom

Under this scenario perfect use of male condom was assumed, characterised by annual failure rate equal to 2%, as reported in a published review.[402] 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 rest LARC methods, combined with male condom or alone, are slightly more effective than perfect use of male condom at one year of use, but at a substantially higher cost (resulting in a range of ICERs between £73,370 and £98,286 per pregnancy averted).

These results are explained by the high discontinuation rates of LARC methods, that lead to use of the average contraceptive method, which is far less effective than perfect use of male condom (failure rates 12.84% versus 2% respectively).

Evidence statement:
Male condom is more cost-effective than LARC methods (used alone or in combination with male condom) when perfect use of male condom is achieved.

8.4.1.2.6 Perfect use of male condom and elimination of discontinuation rates at 1% for LARC methods

This scenario was explored because discontinuation of LARC methods was believed to affect substantially the relative cost-effectiveness between LARC methods and male condom, when perfect use of the latter was assumed. In this case IUD dominates male condom at 4 years of use and above; all other LARC methods (and IUD used for shorter periods of use) are shown to be more effective and also more costly for one year and up to 15 years of use. The additional costs per additional pregnancy averted (ICERs) incurred by LARC methods versus male condom range from £155 (IUS, 10 years of use) to £9,949 (IUS, one year of use).

Evidence statement:
When discontinuation of IUD is eliminated, then IUD is more cost-effective than male condom for periods of use equalling 4 years and above, even when the latter is used perfectly.

8.4.1.2.7 Combination of LARC methods with male condom, perfect use of male condom, and elimination of discontinuation rates at 1% for LARC methods

Under this scenario, combinations of LARC methods with condom are more effective and more costly than male condom alone across all time frames examined. The additional costs per additional pregnancy averted (ICERs) incurred by combinations of LARC methods with male condom versus male condom alone range from £626 (IUD licensed for 8 years, at 8 years of use) to £12,360 (IUS, one year of use).

8.4.1.2.8 Varying discount rates between 0-6%

This scenario was investigated as recommended by NICE guidance on Health Technology Appraisal.[413] Base-case results are not sensitive to changes in discount rate.

Summary of evidence

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

- **Relative cost-effectiveness between LARC and condom is not affected by changes in the ingredient cost of male condom and number of items used annually.**

- **Male condom is more cost-effective than LARC methods (alone or combined with male condom) when perfect use of male condom is achieved, due to high discontinuation rates characterising LARC methods.**

- **Assuming negligible discontinuation rates, LARC alone or combined with condom are more effective and more costly than condom alone, considering perfect use of condom, with the exception of IUD alone, considering perfect use of condom, with the exception of IUD alone, which dominates male condom at 4 years of use and above.**

8.4.2 Comparison of LARC methods with COC

8.4.2.1 Base-case analysis

All LARC methods are associated with smaller number of pregnancies compared to COC across all time periods examined. The IUD and the injectable constantly dominate COC in all time horizons up to 15 years. The IUS and the implant incur an additional cost equal to £533 and £516 per pregnancy averted respectively at one year of use. For longer periods of use, both methods dominate COC. Results for one and up to 4 years of use are shown in table 8.7. Results for longer periods of use, showing the dominance

of LARC methods versus COC over time are not presented.

Table 8.7 Total costs and pregnancies per 1000 women: LARC versus COC

1year of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus COC
Condom	91	230,275	
IUD	18	194,766	LARC dominates
IUS	17	269,610	£533 per additional pregnancy averted
Injectable	36	194,477	LARC dominates
Implant	17	268,162	£516 per additional pregnancy averted

2 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus COC
Condom	190	400,797	
IUD	55	254,746	LARC dominates
IUS	57	334,447	LARC dominates
Injectable	110	345,477	LARC dominates
Implant	62	339,990	LARC dominates

3 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus COC
Condom	289	566,869	
IUD	105	333,845	LARC dominates
IUS	109	414,251	LARC dominates
Injectable	184	492,116	LARC dominates
Implant	122	434,729	LARC dominates

4 years of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus COC
Condom	386	728,470	
IUD	166	426,841	LARC dominates
IUS	167	502,658	LARC dominates
Injectable	258	635,307	LARC dominates
Implant	193	617,484	LARC dominates

Evidence statement:

LARC methods are cost-effective compared with COC across all periods of use examined, starting from 1-2 years of use (depending on the LARC method assessed).

8.4.2.2 Sensitivity analysis

8.4.2.2.1 Changing the ingredient cost and/or duration of follow-up consultations of COC

Using the lowest ingredient cost for COC,[102] 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 slightly the ICER values of the IUS and the implant versus the COC at one year of use.

Evidence statement:
Relative cost-effectiveness between LARC and COC is not sensitive to changes in ingredient cost and/or the duration and frequency of follow-up consultations of COC.

8.4.2.2.2 Variability in effectiveness rates of LARC methods

As with male condom, no sensitivity analysis was undertaken to examine the impact of uncertainty in the failure rates of LARC methods on the base-case results. Small (as anticipated) changes in LARC failure rates are not expected to have any impact on the base-case results.

8.4.2.2.3 Variability in discontinuation rates of LARC methods

Decreasing discontinuation rates of LARC methods would favour their relative cost-effectiveness versus COC. An increase in LARC discontinuation rates was not considered, since the rates reported were thought to be already relatively high.

8.4.2.2.4 Elimination of discontinuation rates at 1% for both LARC and COC

The rationale for carrying out such an analysis is to investigate whether discontinuation is an important driver of relative cost-effectiveness between LARC methods and COC. Due to lack of high quality data on ranges of discontinuation rates for both comparators, negligible rates of discontinuation have been assumed and the impact of such a scenario on the base-case results is examined.

Results are not affected by this hypothesis, probably because the base-case scenario uses similarly high discontinuation rates for both LARC and COC; therefore, elimination of discontinuation affects both comparators in a similar degree.

Evidence statement:
Relative cost-effectiveness between LARC methods and COC is not sensitive to elimination of discontinuation rates at 1% for both comparators.

8.4.2.2.5 Elimination of discontinuation rates at 1% for COC only

Base-case results remain robust when elimination of annual discontinuation rates at 1% for COC only is assumed.

Evidence statement:
LARC methods are more cost-effective than COC, even when high adherence to COC (99% annually) is assumed.

8.4.2.2.6 Perfect use of COC

Perfect use of COC is characterised by annual failure rate equal to 0.3%, as reported in a published review.[402] Results remain relatively robust regarding IUD and IUS when perfect use of COC is assumed. IUD dominates COC for

time frames equal to 2 years of use and over, while the dominance of IUS over COC starts at 4 years of use. The implant remains more effective, but it is also more costly. Its ICER compared to COC ranges from £8,028 per pregnancy averted (for one year of use) to £116 per pregnancy averted (for 12 years of use), whereas it dominates COC for 14 and 15 years of use. When COC is perfectly used, it dominates the injectable across all time horizons examined.

Evidence statement:
IUD and IUS are more cost-effective than COC, even when perfect use of COC is achieved, after 1 and 3 years of contraceptive use, respectively. COC becomes more cost-effective than the injectable when it is characterised by perfect use.

8.4.2.2.7 Perfect use of COC and elimination of discontinuation rates at 1% for both LARC and COC

Results obtained when perfect use of COC is assumed are sensitive to elimination of discontinuation rates for both LARC and COC (less sensitive for IUD and IUS, and for longer periods of use). Results under these assumptions become significantly more favourable for COC than in the previous scenario. COC remains, in principle, less effective than LARC methods, but it is also less costly, at least for short periods of use (the exact period of time depending on which LARC method is serving as the comparator).

8.4.2.2.8 Varying discount rates between 0-6%

Base-case results are not sensitive to changes in discount rate.

Summary of evidence

- **LARC are more cost-effective compared to COC, even for short periods of use, starting from 1-2 years.**

- **Relative cost-effectiveness between LARC methods and COC is not sensitive to changes in the ingredient cost and/or the duration and frequency of follow-up consultations of COC.**

- **Relative cost-effectiveness between LARC methods and COC remains robust when elimination of discontinuation rates at 1% annually is assumed for both LARC and COC, or when elimination of discontinuation at 1% annually is assumed for COC only.**
- **IUD and IUS are more cost-effective than COC, even when perfect use of COC is assumed, after 1 and 3 years of contraceptive use respectively. In contrast, perfect use of COC is more cost-effective than use of the injectable.**

8.4.3 Comparison of LARC methods with female and male sterilization

8.4.3.1 Base-case analysis

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 £37,435 (versus IUD) for one year of use. However, these incremental costs decrease as 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 and the implant, at 6 years of use when the comparator is the IUS, 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 £14,331 per pregnancy averted, which falls at £3,422 at 2 years of use (all other ICERs are lower than £2,000 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 sterilization over LARC methods persistes thereafter, as expected, up to the maximum time frame examined (15 years).

Results for one and up to 7 years of use are shown in table 8.8. Results for longer periods of use, showing the persisting dominance of female and male sterilisation over LARC methods over time, are not presented.

Table 8.8 Total costs and pregnancies per 1000 women: LARC versus female and male sterilization

1 year of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
IUD	18	194,766	£37,435/preg averted	£14,331/preg averted
IUS	17	269,610	£35,102/preg averted	£10,668/preg averted
Injectable	36	194,477	£15,925/preg averted	£6,931/preg averted
Implant	17	268,162	£34, 216/preg averted	£10,521/preg averted
F Steril	5	692,462		
M Steril	2	435,461		

2 years of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
IUD	55	254,746	£9,022/preg averted	£3,422/preg averted
IUS	57	334,447	£7,079/preg averted	£1,845/preg averted
Injectable	110	345,477	£3,381/preg averted	£844/preg averted
Implant	62	339,990	£6, 415/preg averted	£1,616/preg averted
F Steril	6	694,821		
M Steril	2	436,254		

3 years of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
IUD	105	333,845	£3,713/preg averted	£1,003/preg averted
IUS	109	414,251,	£2,792/preg averted	£214/preg averted
Injectable	184	492,116	£1,161/preg averted	M sterilization dominates
Implant	122	434,729	£2,286/preg averted	£19/preg averted
F Steril	7	697,100		
M Steril	2	437,019		

4 years of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
IUD	166	426,841	£1,735/preg averted	£67/preg averted
IUS	167	502,658	£1,243/preg averted	M sterilisation dominates
Injectable	258	635,307	£256/preg averted	M sterilisation dominates
Implant	193	617,484	£443/preg averted	M sterilisation dominates
F Steril	9	699,301		
M Steril	3	437,759		

5 years of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
IUD	232	527,405	£783/preg averted	M sterilisation dominates
IUS	228	595,426	£485/preg averted	M sterilisation dominates
Injectable	332	775,044	F sterilisation dominates	M sterilisation dominates
Implant	268	727,788	F sterilisation dominates	M sterilisation dominates
F Steril	10	701,429		
M Steril	3	438,474		

6 years of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
5-year IUD	299	664,954	£133/preg averted	M sterilisation dominates
8-yar IUD	299	627,521	£263/preg averted	M sterilisation dominates
IUS	290	757,793	F sterilisation dominates	M sterilisation dominates
Injectable	405	911,328	F sterilisation dominates	M sterilisation dominates
Implant	340	835,304	F sterilisation dominates	M sterilisation dominates
F Steril	11	703,484		
M Steril	4	439,165		

7 years of use	Total pregnancies	Total costs	ICER Female sterilization versus LARC method	ICER Male sterilization versus LARC method
5-year IUD	365	762,773	F sterilisation dominates	M sterilisation dominates
8-yar IUD	365	724,963	F sterilisation dominates	M sterilisation dominates
IUS	351	847,451	F sterilisation dominates	M sterilisation dominates
Injectable	477	1,044,173	F sterilisation dominates	M sterilisation dominates
Implant	411	990,522	F sterilisation dominates	M sterilisation dominates
F Steril	12	705,470		
M Steril	4	439,832		

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 and the implant), 6 years (compared to the IUS) 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.

Both types of sterilisation are likely to be more cost-effective than LARC methods for shorter periods of use than the above reported.

8.4.3.2 Sensitivity analysis

8.4.3.2.1 Changes in cost of female and male sterilisation

20% increase in sterilisation costs: Base-case results are moderately affected by this scenario in the short term. Female sterilisation becomes dominant over all LARC methods at 8 years of use, whereas the same applies to male sterilisation at 5 years of use.

Evidence statement:
The relative cost-effectiveness between sterilisation (both female and male) and LARC methods is only moderately sensitive to 20% changes in sterilisation costs in the short term.

8.4.3.2.2 Variability in effectiveness rates of LARC methods and/or female and male sterilisation

The impact on the results of altering values of the base-case failure rates related to one or both comparators was not examined in a sensitivity analysis. However, it was thought that a scenario involving changes in effectiveness rates would be meaningful only after assuming negligible discontinuation of LARC, since the latter was thought to be a more important driver of relative effectiveness (and, in effect, cost-effectiveness) between LARC methods and sterilisation.

8.4.3.2.3 Elimination of discontinuation rates of LARC methods at 1%

It was believed that the high discontinuation rates of LARC methods were likely to affect significantly the relative cost-effectiveness between LARC methods and sterilisation, considering that sterilisation methods are non-reversible, and therefore no discontinuation occurs (reversal of sterilisation was not considered in the analysis). A sensitivity analysis based on discontinuation rates of 1% was carried out to investigate the impact of discontinuation associated with LARC methods on the relative cost-effectiveness between them and sterilisation (female and male).

As expected, base-case results are very sensitive to this scenario, especially for shorter periods of contraceptive use. Elimination of discontinuation favours LARC methods and increases their relative cost-effectiveness compared with female and male sterilisation. Up to 4-6 years of use, both female and male sterilisation are characterised by substantially high ICERs compared to LARC methods (e.g. the ICER of female sterilisation versus IUD for one year of use is £854,665 per pregnancy averted) or are even dominated by LARC methods. Results are still sensitive but in a lower degree for longer periods of use considered. The magnitude of sensitivity depends also on the specific LARC method serving as comparator.

Evidence statement:
The level of discontinuation associated with LARC methods is an important determinant of the relative cost-effectiveness between LARC methods and female/male sterilisation.

8.4.3.2.4 Varying discount rates between 0-6%

Results are slightly sensitive to changes in discount rate. This was expected, as practically all method costs associated with sterilisation occur in the first year of use (undiscounted costs), whereas LARC method costs are more evenly distributed over time (different timing in costs means that costs are

processed with different discount factor and this, in turn, results in a different present value attached to them).

Summary of evidence

Female and male sterilisation are more cost-effective than all LARC methods for 7 and 5 years of contraceptive use and above respectively, and, depending on the LARC method, they are also more cost-effective for shorter periods of use as well (starting from 5 and 3 years respectively).

- **Relative cost-effectiveness between LARC methods and sterilisation is only moderately sensitive to 20% changes in sterilisation costs.**

- **The level of discontinuation associated with LARC methods is an important determinant of the relative cost-effectiveness between LARC methods and female/male sterilisation.**

8.4.4 Comparisons between LARC methods

8.4.4.1 Base-case analysis

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 IUD ,the implant and the IUS compared to the injectable for one year of use are £16, £3,905 and £3,908 per pregnancy averted respectively.

The *implant* is dominated by the IUD and the IUS for periods of use between 2 and 15 years. For one year of use, the implant is slightly more effective than the IUD, but at a substantially additional cost equal to £82,095 per additional

pregnancy averted. The IUS is more costly and slightly more effective than the implant for one year of use, with an ICER reaching $4,087 per pregnancy averted.

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 decreases over time, starting from £18,583 per pregnancy averted for 5 years of use, and falling at £1,178 and £1,889 per pregnancy averted, compared to 5-year and 8-year licensed IUD respectively, 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 £59,950 per pregnancy averted.

The *IUD* dominates all other LARC methods for time frames between 2-4 years of use. For longer periods and up to the maximum 15-year time horizon examined, the IUD still dominates the injectable and the implant.

Results throughout 15 years of contraceptive use are shown in table 8.9. For each time frame examined LARC methods are ranked from the least to the most effective. The last column reports the ICERs in the case of one method being more effective and more costly than its comparator (no such case exists between 2 and 4 years of use). All cases of dominance are reported in a separate column.

Table 8.9 Total costs and pregnancies per 1000 women: comparisons between LARC methods

1 year of use	Total pregnancies	Total costs	Incremental Cost Effectiveness Ratio LARC method versus COC
Injectable	36	194,477	
IUD	18	194,766	IUD versus injectable: £16/pregnancy averted
Implant	17*	268,162	Implant versus Injectable: £3,905/pregnancy averted Implant versus IUD: £82,095/pregnancy averted
IUS	17*	269,610	IUS versus Injectable: £3,908/pregnancy averted IUS versus IUD: £59,950/pregnancy averted IUS versus implant: £4,087/pregnancy averted

*The number of total pregnancies is slightly lower for the IUS than the Implant; number presented are rounded to the nearest whole number.

2 years of use	Total pregnancies	Total costs	Dominance
Injectable	110	345,477	Dominated by IUD, IUS, Implant
IUD	62	339,990	Dominated by IUD, IUS
Implant	57	334,447	Dominated by IUD
IUS	55	254,746	DOMINANT

3 years of use	Total pregnancies	Total costs	Dominance
Injectable	184	492,116	Dominated by IUD, IUS, Implant
IUD	122	434,729	Dominated by IUD, IUS
Implant	109	414,251	Dominated by IUD
IUS	105	333,845	DOMINANT

4 years of use	Total pregnancies	Total costs	Dominance
Injectable	258	635,307	Dominated by IUD, IUS, Implant
IUD	193	617,484	Dominated by IUD, IUS
Implant	167	502,658	Dominated by IUD
IUS	166	426,841	DOMINANT

5 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	332	775,044	Dominated by IUD, IUS, Implant	
Implant	268	727,788	Dominated by IUD, IUS	
IUD	232	527,405		IUS versus IUD: £18,583/pregnancy averted
IUS	228	595,426		

6 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	405	911,328	Dominated by IUD, IUS, Implant	
Implant	340	835,304	Dominated by IUD, IUS	
5-year IUD	299	664,954		IUS versus 5-year IUD: £10,076/preg averted
8-year IUD	299	627,521		IUS versus8-year IUD: £14,138/pregnancy averted
IUS	290	757,793		

7 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	477	1,044,173	Dominated by IUD, IUS, Implant	
Implant	411	990,522	Dominated by IUD, IUS	
5-year IUD	365	762,773		IUS versus 5-year IUD: £5,816/pregnancy averted
8-year IUD	365	724,963		IUS versus 8-year IUD: £8,413/pregnancy averted
IUS	351	847,451		

8 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	548	1,173,598	Dominated by IUD, IUS, Implant	
Implant	479	1,091,947	Dominated by IUD, IUS	
5-year IUD	429	857,660		IUS versus 5-year IUD: £3,916/pregnancy averted
8-year IUD	429	819,701		IUS versus 8-year IUD: £5,844/pregnancy averted
IUS	409	934,719		

9 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	619	1,299,630	Dominated by IUD, IUS, Implant	
Implant	545	1,190,418	Dominated by IUD, IUS	
5-year IUD	491	949,856		IUS versus 5-year IUD: £2,839/pregnancy averted
8-year IUD	491	944,074		IUS versus 8-year IUD: £3,075/pregnancy averted
IUS	466	1,019,641		

10 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	688	1,422,305	Dominated by IUD, IUS, Implant	
Implant	610	1,330,398	Dominated by IUD, IUS	
5-year IUD	551	1,039,435		IUS versus 5-year IUD: £2,147/pregnancy averted
8-year IUD	551	1,033,899		IUS versus 8-year IUD: £2,337/pregnancy averted
IUS	522	1,102,274		

11 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	756	1,541,661	Dominated by IUD, IUS, Implant	
Implant	672	1,423,203	Dominated IUD, IUS	
5-year IUD	610	1,155,833		IUS versus 5-year IUD: £2,452/pregnancy averted
8-year IUD	610	1,120,988		IUS versus 8-year IUD: £3,485/pregnancy averted
IUS	576	1,238,565		

12 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	823	1,657,742	Dominated by IUD, IUS, Implant	
Implant	733	1,513,285	Dominated by IUD, IUS	
5-year IUD	667	1,240,646		IUS versus 5-year IUD: £2,005/pregnancy averted
8-year IUD	667	1,205,584		IUS versus 8-year IUD: £2,927/pregnancy averted
IUS	629	1,316,870		

13 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	888	1,770,596	Dominated by IUD, IUS, Implant	
Implant	792	1,639,531	Dominated by IUD, IUS	
5-year IUD	722	1,323,000		IUS versus 5-year IUD: £1,663/pregnancy averted
8-year IUD	722	1,287,756		IUS versus 8-year IUD: £2,500/pregnancy averted
IUS	680	1,393,053		

14 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	953	1,880,276	Dominated by IUD, IUS, Implant	
Implant	849	1,724,395	Dominated by IUD, IUS	
5-year IUD	776	1,402,913		IUS versus 5-year IUD: £1,395/pregnancy averted
8-year IUD	776	1,367,573		IUS versus 8-year IUD: £2,162/pregnancy averted
IUS	730	1,467,129		

15 years of use	Total pregnancies	Total costs	Dominance	Incremental Cost-Effectiveness Ratios
Injectable	1016	1,986,835	Dominated by IUD, IUS, Implant	
Implant	905	1,806,752	Dominated by IUD, IUS	
5-year IUD	828	1,480,523		IUS versus 5-year IUD: £1,178/pregnancy averted
8-year IUD	828	1,445,105		IUS versus 8-year IUD: £1,889/pregnancy averted
IUS	778	1,539,165		

Evidence statement:

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 and the implant

for 2 and up to 15 years of contraceptive use.

IUS is more cost-effective than the implant and the injectable between 2 and 15 years of contraceptive use.

The implant is more cost-effective than the injectable for 2-15 years of contraceptive use.

The injectable is less cost-effective than any other LARC method for 2-15 years of contraceptive use.

8.4.4.2 Sensitivity analysis

8.4.4.2.1 Variability in effectiveness rates of LARC methods

Although uncertainty surrounding effectiveness rates of LARC methods may affect their relative cost-effectiveness, this was not tested in a sensitivity analysis, as no ranges of values appropriate for this purpose could be identified by the GDG.

8.4.4.2.2 Variability in discontinuation rates of LARC methods – elimination of discontinuation rates at 1%

Discontinuation rates of LARC methods were considered to be an important parameter in determining the relative cost-effectiveness between methods. In order to test this hypothesis, and since appropriate ranges of values could not be identified for this purpose, a sensitivity analysis was carried out using a negligible discontinuation rate of 1% for all LARC methods. This enables evaluation of the relative cost-effectiveness between LARC methods after eliminating the impact of discontinuation.

Under this scenario, the *injectable* dominates IUS for one year of use, but is dominated by IUS for longer periods. In addition, it is also dominated by the implant for 2-15 years examined. For one year of use, the implant is more

costly and more effective than the injectable, with an ICER of £90,521 per pregnancy averted. The injectable dominates IUD for one year of use; for longer periods it is more effective but more costly, with ICERs ranging from £21,466 (2 years) to £52,731 (15 years, versus 8-year licensed IUD) per pregnancy averted.

The *implant* is the most effective among LARC methods. For time periods between 2-15 years, it dominates the injectable. Between 1-3 years and at 6 years of use, it dominates IUS. For the rest periods examined, its ICER compared to IUS ranges from £15,447 (12 years) to £44,337 (4 years) per pregnancy averted. Implant is constantly more expensive than the IUD, with ICERs ranging from £6,012 (3 years) to £20,665 (7 years, versus 8-year licensed IUD) per pregnancy averted.

The *IUS* dominates the injectable for 2 years of use and above, but it is dominated by it at one year of use. IUS is dominated by the implant between 1-3 years of use, and also at 6 years of use. In all other time frames examined it is less effective but also less costly than the implant. IUS is more effective and more costly than IUD, with ICERs ranging from £6,742 (5 years) to £20,829 (6 years, versus 8-year licensed IUD) per pregnancy averted.

IUD is constantly less effective but also less costly among LARC methods, with the only exception at one year of use, where IUD is dominated by the injectable (which is less costly than IUD, in this case).

Evidence statement:
Relative cost-effectiveness between LARC methods is significantly affected by the high discontinuation rates associated with LARC use.

8.4.4.2.3 Varying discount rates between 0 – 6%

The results are slightly sensitive in changes in discount rates. The ranking of methods according to effectiveness and all cases of dominance are not affected. The only changes are observed in the ICERs between IUS and IUD;

a discount rate of 6% increases the ICERs modestly, whereas no discounting (rate 0%) results in a small reduction in the ICERs.

Summary of evidence

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 and the implant for 2 years of use and above.

- **After one year of use, IUS is more cost-effective than the implant and the injectable.**

- **The implant is more cost-effective than the injectable for periods of use starting at 2 years and over.**

- **The injectable is less cost-effective than any other LARC method for 2 years of use and above.**

- **The level of discontinuation is an important driver of the relative cost-effectiveness between LARC methods.**

8.5 Caveats – further considerations

The analysis was based on best evidence available. Validity of 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. Nevertheless, base-case results are robust under most scenarios examined in sensitivity analysis.

Results refer to the general UK population of women of reproductive age. Findings might be different for sub-groups within this population who have different characteristics and needs. Female sterilisation is not a realistic option for women who may wish to retain their fertility. Comparison of LARC methods with male sterilisation presupposes the couple as “unit of protection” and not

the woman alone. This means that a woman is required to be in a stable, long-term relationship with one man so that such a comparison is meaningful. Users' compliance is another issue that has to be taken into account at the interpretation of the results. Perfect use of the COC (which has been demonstrated to be more cost-effective compared to some LARC methods) requires perfect compliance with the method. This may not be the case for certain sub-groups of the population, such as adolescents {Emans 1987} or women with no established regular routine.[416] The use of LARC methods in this case is more cost-effective, since their effectiveness in practice does not depend on users' compliance.

Finally, side effects as well as other non-contraceptive benefits (e.g. management of menstrual disorders) associated with use of LARC methods, which were not possible to consider in the economic analysis, should also be taken into account when choices regarding contraceptive method use are made.

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. [GPP]		
Women considering a LARC method 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 • non-contraceptive benefits • the procedure for initiation and removal/discontinuation • duration of use • when to seek help while using the method.[GPP]		
All healthcare 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 [GPP]		
All healthcare 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. [GPP]		

All healthcare professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. [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

Appendix A

Information for the public (This will be available in the second draft of this guideline)

Appendix B

Clinical evidence forest plots

Figure B.1 Comparison between Multiload Cu375 and CuT380A showing accidental pregnancy rates

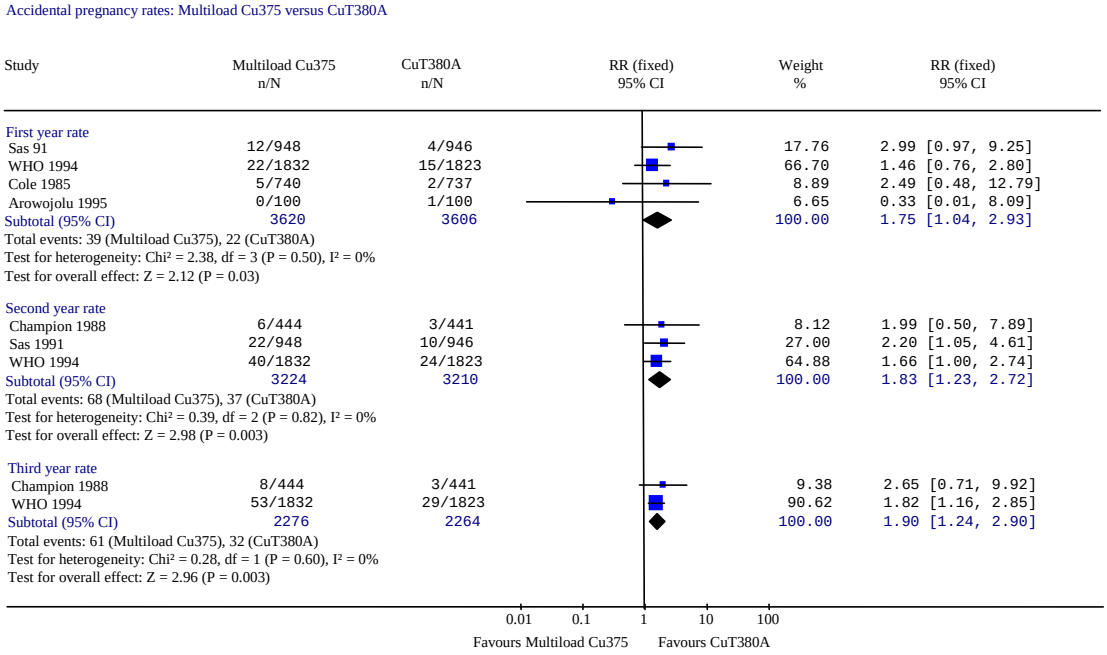


Figure B.2 Comparison between Multiload Cu250and CuT380A showing accidental pregnancy rates

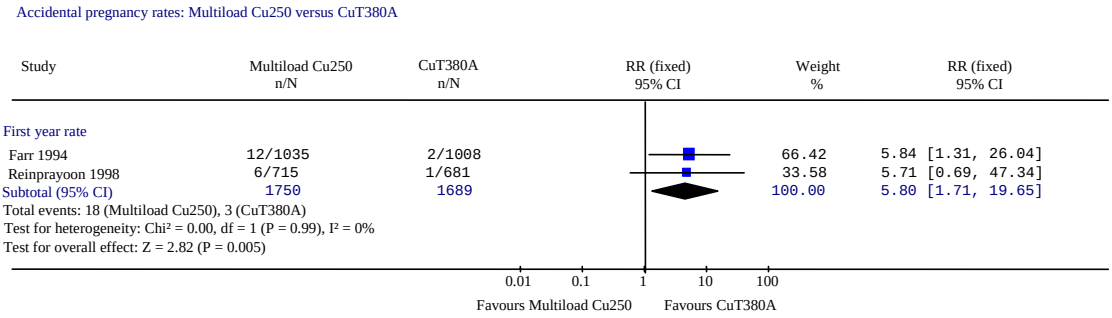
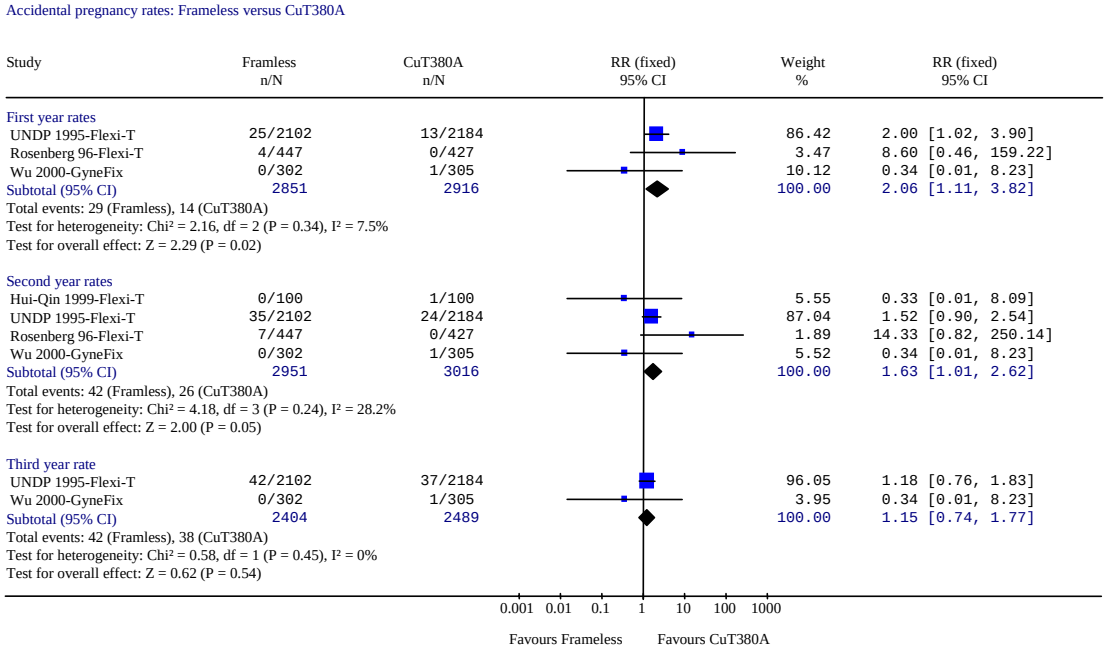


Figure B.3 Comparison between frameless IUDs and CuT380A showing accidental pregnancy rates



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 [66] 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]

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 [53] 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 ' versus '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%

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 [45] 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 [417] 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[55] 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% versus 32% Due to othe medical events (weight gain, vomiting, dizziness, depression and loss of libido) 6.3% versus 7.4% Total discontinuation: 17% versus 43%	Not stated	

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 [267] 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% versus 26% Due to: Missing injection 0.5% versus 4% Personal reasons: 4% versus 8.5% Lost to follow-up 0% versus 8.5% Protocol violation: 1% versus 0% Total discontinuation: 11.3% versus 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 [57] 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 versus WHO versus categories 85% versus 855 versus 77% Significant improvement: FDA versus WHO versus categories 20% versus 19% versus 37% FDA versus WHO versus categories 19% versus 15% versus 6%	Not stated	Clear method of randomisation and concealment

Chapter 4 Copper Intrauterine 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[110] 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[111] 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 due to heavy menstrual bleeding C)	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% versus 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
								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[105] 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 D) Pain Events after insertion (%): A) PID B) Hospitalisation due to bleeding	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 During insertion: A) T380Ag: 0 ML375: 0.2	Family Health International and the US Agency for International Development	A continuation of the Cole study[111] Random allocation by opaque envelopes prepared by Family Health International; mean age and mean parity were higher in the ML375 group (27.5 versus. 26.4 years, p<0.05; 1.7 versus. 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
									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[112] 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[113] 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 since parturition or abortion, history of ectopic pregnancy, recent STI, undiagnosed genital	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 pregnancy B) Ectopic C) Expulsion	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 C) T380A: 3.8 (0.5) ML375: 3.6 (0.4) Continuation rate:	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
				tract bleeding, known/suspected genital tract malignancy, multiple fibromyomas associated with menstrual disorders, evidence of anaemia, and history of hytidaform mole in last pregnancy				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[114] 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 displacement C) Medical removal for bleeding or pain	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) Discontinuation rate: For T380A: 9.8 (1.2) For ML259: 12.5 (1.3)	Family Health International and the US Agency for International Development	Random allocation by sealed envelopes IUD inserted during the interval 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
								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	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*		
Farr 1994[115] 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 removal for bleeding or pain Discontinuation rate	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) ML250: 2.8 (0.54) Discontinuation rate: For T380A: 9.9 (0.98) For ML250: 11.4 (1.02)	Family Health International and the US Agency for International Development	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
								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	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*		
Rosenberg 1996 [118] 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 Exclusions: Nulliparous, history of ectopic pregnancy, PID, or infection with gonorrhoea or Chlamydia, diabetes, jaundice or anaemia	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 removal for PID Continuation rate	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) B) 2.0 (0.7) C) 11.4 (2.3) D) 1.0 (0.6) Continuation rate: 78.3 (4.7)	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
UNDP 1995[418] 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[120] 6 centres in China	Multicentre RCT	1+	607	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,	TCu380A (n=305)	GyneFix (n=302)	3 years	Cumulative discontinuation rates* at 1, 2 and 3 years due to: A) Pregnancy B) Expulsion C) Perforation D) Medical removal E) Medical	At 1 year (281 and 289 women remaining for T380A and GyneFix respectively) A) T380A: 0.34 GyneFix: 0 B) T380A: 4.63 GyneFix: 2.67 C) T380A: 0 GyneFix: 0 D) T380A: 3.08	Contrel Europe	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
				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				removal for bleeding or pain F) Medical removal for PID **no standard errors reported*	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 GyneFix: 0 ** difference between the two devices significant at p = 0.32* *** difference between the two devices significant at p = 0.018*		

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
Hui-Qin 1999[121] 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[419]	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[418] and Rosenberg 1996[118] for relevant information extracted from these trials on devices currently licensed in the UK Only 1 RCT compared devices that are currently licensed in the UK; please see entry for Wu 2000[120]
Van Kets 1995[161] Study site not	RCT	1-	600	Nulliparous (n=97) and parous (n=503) women, aged 18 to 45 years, requesting	TCu380A (n=300)	Cu-Safe300 (n=300)	3 years	Cumulative discontinuation rates per 100 women (95% CI)	At 1 year: A) T380A: 0.8 (0.0, 3.0) CuSafe: 1.5 (0.4, 3.7) B) T380A: 0	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
specified although authors and ethical approval came from Belgium				intrauterine contraception Exclusions: < 6 weeks since last pregnancy				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*	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) 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)		

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: 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 [127] 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 H) No of women completing interval	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 versus 23.5 Reduced bleeding: 3.1 versus 10.9 Increased bleeding: 7.2 versus 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		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
Geyoushi 2002[124] 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	
Wilson 1989[420] 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	MLCu375	MLAgCu250	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	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	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

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
				copper or silver allergy or disorder of copper metabolism				insertion C) Fainting	MLAg250: 2.0 C) ML375: 1.3 MLAg250: 0.7 ** difference between the two devices significant at p<0.05*		
Wilson 1992[421] New Zealand	Multicentre RCT	1-	Not stated (!!)	Women choosing an intrauterine device as contraception See Wilson[420] (above) for exclusion criteria	MLCu375	MLAgCu250	3 years	Cumulative discontinuation rates per 100 women (SE) at 2 and 3 years due to: A) Pregnancy B) Expulsion C) Medical removal for bleeding or pain D) Medical removal for personal reasons E) Planning pregnancy Loss to follow-up (%)	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) 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)	Not stated	A continuation of previous study by Wilson[420] The number of women originally recruited for each arm was 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
WHO 1990[162] Study contained data from 3 RCTs conducted in 24 centres in 14 countries (mostly developing), but data only shown from first (9 centres) and second trial (13 centres); third trial did not include any devices currently licensed in the UK	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, 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	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 D) Perforation E) Medical removal for bleeding or pain Discontinuation rates Loss to follow-up Complications during insertions (%): A) Failure	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: 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	Not stated	Computer generated random allocation by sealed envelopes in balanced in blocks of six or ten
Cox 2002[116] UK	Multicentre observational	3	574	Parous women, aged 18 to 45 years, requesting intrauterine contraception in general practice and at family planning clinics Exclusions:	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	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	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
				nulliparous, second or subsequent fitting, IUD fitted as emergency contraception, pregnant at fitting, <6 weeks since last pregnancy, concomitant contraception				C) Perforation D) Medical removal for bleeding or pain E) PID** Discontinuation rate Loss to follow-up ** 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*	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 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[117]	Multicentre	3	400	Women volunteers,	NovaT380	No	2 years	Cumulative	At 1 year (341 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
3 centres in Finland	observational			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 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		comparison group		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 removal for pain E) Planning pregnancy F) PID Discontinuation rate	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 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)	stated	All insertions performed within 7 days of onset of menstruation
Rivera 1999[144] Cameroon, Chile, Egypt, El Salvador, Malaysia, Mexico, Nigeria, Pakistan, Peru, Philippines, Sri Lanka,	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	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)	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
Thailand, Turkey, and Venezuela								rates at 1 year: A) All reasons B) Expulsion C) Bleeding or pain D) Personal reasons Effect of parity on discontinuation rates at 1 year: A) All reasons B) Expulsion C) Bleeding or pain D) Personal reasons	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) 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[422] 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	Case note review and postal questionnaire**	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	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
				IUD expulsion or pain; parous women who preferred a frameless device ** n=26 women used GyneFix for emergency contraception; data for these women were not presented separately and therefore could not be excluded*	*** 183 (85%) completed questionnaires*				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 due to pregnancy (conception prior to insertion)		
Dennis 2001[423] 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[424] 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[143]	RCT	1+	806	Women choosing the IUD as a contraceptive device	TCu380A (n=806)	TCu380S* (n=762)	5 years	Cumulative discontinuation rates per 1000	At 1 year: A) 0.1 (0.1) B) 4.5 (0.8)	Ortho Pharmaceutical	Computer generated random allocation in

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
Brazil				Exclusions: Nulliparouos, history of PID		* Data not shown for this device		women** (SE) at 1, 3 and 5 years due to: A) Pregnancy B) Expulsion C) Medical removal for bleeding or pain Continuation rate Loss to follow-up	C) 4.3 (0.8) Continuation rate: 88.0 (1.2) 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	Ltd in Canada donated IUDs	sealed opaque envelopes All insertions performed during the first 7 days of menstruation ** text states per 1000 women, but I suspect this is actually per 100 women
Kivijarvi 1983[425] 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 (%)	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:	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
								* *none were ectopic*	For ML250: 6.7 For ML250 short: 4.6		
UNDP 1997[104] 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[106] 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	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)	Not stated	Study contained data on a third device which was not included as it is

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
								to: A) Pregnancy B) Expulsion C) Medical removal for bleeding or pain D) PID Pearl index for unintended pregnancy Discontinuation rate	C) ML375: 9.6 (2.1) 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:		not currently 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 ML375: 0.9 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[151] 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*	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
									prior to insertion significant 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[152] 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[151] Method of random allocation not specified
Merki-Feld 2000[174] Switzerland	Retrospective	3	156	All women who used LNG-IUD or ML375 IUD in a family planning clinic with no	MLCu375 (n=104)	LNG-IUD (n=52)		Number of women followed for at least 10 months (others not	Women included in final analysis: MLCu375: 65 LNG: 34	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
				evidence of ALO at time of insertion				included in final analysis) Detection of ALOs using PAP stained cervical smears by length of IUD use (%)	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[179] 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[181] 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 last month, any organic pelvic disease	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
Harrison-Woolrych 2003[182] 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[196] 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 2002[426] UK	Observational	3	200	Nulliparous (n=136) and parous (n=64) women fitted with GyneFix at a family planning clinic in London	GyneFix	No comparison group	1 year	Discontinuation rate per 100 women (95% CI) at one year due to: A) Pregnancy B) Expulsion	At 1 year (121 women remaining): A) 0 B) 0.08 (0.05, 0.13) C) 0.09 (0.05, 0.14) Planning pregnancy: 3	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
								C) Medical removal for bleeding or pain Number removed due to planning pregnancy Complications during insertion (%): A) Perforation	During insertion: A) 0.5		
Snowden 1982[427] 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) 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)	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
									** could not be calculated due to insufficient numbers remaining*		
Martinez 2002[428] 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[160] 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[429] Greece	Observational	3	200	Parous married women requesting IUD as contraception Exclusions: allergic reaction to copper, history of previous ectopic pregnancy, history of STI, history of PID, genital tract malformation, blood clotting disorders	MLCu250	No comparison group	36 months	PID cases	No cases diagnosed	Not stated	IUDs inserted on the last day of menstruation
Farley 1992[178]	Secondary data	2	22908	Women were from 12 RCTs on IUD use	Copper T 380A	No comparison	Various	A) No. of insertions	A) CopperT: 2795 ML375: 1060	WHO Special	Data was from

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
Studies from Europe, Asia, Americas and Africa	analysis			Exclusions: nulliparous, history of STI in past 6 months, previous PID, genital tract malformation or malignant disease, hytidoform mole in previous pregnancy	MLCu375 MLCu250	group		B) PID cases C) PID rate per 1000 women-years D)Risk ≤ 20 days after insertion E) Age < 25 years	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)	Programme fo Research, Development, and Research Training in Human Reproduction and G.D. Searle Company	
Delbarge 2002[430] 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, undiagnosed genital tract bleeding, congenital genital tract malformation, known/suspected genital tract malignancy, multiple uterine fibromyomas associated with menstrual disorders,	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 ** Nulliparous women conceived significantly earlier than parous women at p=0.007*	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
				evidence of anaemia, and history of hytidaform mole in last pregnancy							
Martin-Loeches 2003 [155] 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 Femal e 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
Hubacher 2001 [191] 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 versus infertile controls: OR 1.0 (0.6 to 1.7) Tubal occlusion versus pregnant controls OR 0.9 (0.5 to 1.6)	USAID	

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
Chi 1990 [194]	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) 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	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
Avecilla-Palau et al (2003) [195] 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 versus <300mm versus >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 [206] 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 1997 [150] Brazil	Cohort	2-	481	women with T shaped CuIUDs for at least 6 months (T-Cu 200 or T-Cu 380)		Women with no complaints (n=245)	Women with complaints (n=236)	position of the TCu as imaged by vaginal USS	No correlation		A secondary analysis [431] of this data suggests that position is influenced by growth and thinning of endometrium
Sinei 1998 [214] 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)	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% versus 0.2% E) 4.2% versus 3.8% F) 2.1% versus 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

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
								Expulsions			infected women more likely to be single, in polygamous marriage, have more than one sexual partner (p<0.05)
Morrison 2001 [215] Kenya	Follow-up prospective cohort study from Sinei 1998 [214] 24 months	2+		649 women requesting IUD and met eligibility criteria	See Sinei 1998 [214]			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

Chapter 5 Progestogen only intrauterine system

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 [128] associated references: [129-133] 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 versus 72.8	US Agency for International Development, UN Funds for Population Activities (UNFPA) Rockefeller Foundation etc	

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 versus 3.0 4.4. versus 0.1 0.7 versus 2.0 2.9 versus 1.8 0.6 versus 0.1 0.7 versus 0.4 No significant difference at 7 years: 0.1 versus 0.2 <0.1 v 0.1 0.1 versus 0.1 cervical: 0.0 versus <0.1 uterine: 0.1 versus 0.0		

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	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 versus 8.0 1.3 versus 3.3 1.2 versus 1.1 0.4 versus 0.4 0.4 versus 0.8 0 versus 2 at 7 years 0.7 versus 0.7 Significant difference: 5.3 versus 7.7 No significant difference: 0.0 versus 0.1		

								Return of fertility: Pregnancy rate	Follow- up of 110 women after removal 96.4% versus 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 [134] Associated references: [135-137;140;141] 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% versus 71.2% at 1 year 86.6% versus 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 [432]

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 [432] 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 [134]

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 [139] Associated references: [138;140] 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 breastfeeding 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 [109]

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 [224] 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)

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%		

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 [231] 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% versus 88% versus 87% higher in women < 30 years	Not stated	

Chapter 6 Progestogen only Injectable contraceptives

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 [254] 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 versus 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.

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[250] 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% versus 0.4% NET-EN (60 day), versus 0.6% NET-EN (84 day) at 1 year; 0.4% versus 0.4% versus 1.4% at 2 years 11.9% versus 6.8% versus 8.4% at 1 year; 24.2% versus 14.7% versus 14.6% at 2 years 15.0% versus 13.6% versus 13.7% at 1 year; 18.8% versus 18.4% versus 21.8% at 2 years 51.4% versus 49.7% versus 50.3% at 1 year; 73.5% versus 70.7% versus 72.4% at 2 years Abdominal distension or discomfort 1.1/100 woman-years versus 0.6 versus 0.3; weight gain 2.1 versus 1.6 versus 0.8 kg/100 woman-years Systolic (mmHg) -3.0 versus -2.5 versus +0.1; diastolic -1.6 versus -1.8 versus -0.4 at 2 years +3.3 kg versus +3.3 versus +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 versus 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 [251] 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 versus 3.6±0.7/100 woman-years 7.7 versus 9.5/100 woman-years 23.4±1.7 versus 16.9±1.4/100 woman-years 11.5 versus 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 versus 420.7 woman-years in the DMPA versus 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

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 [252] 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 versus 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 versus 4391 cycles in DMPA and NET-EN groups respectively.
O'Dell 1998 [253] 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% versus 30% p<0.05; irregular bleeding 49% versus 12% p<0.05, headache 39% versus 21%, fatigue 33% versus 9% p<0.05; mood changes 29% versus 9%, p<0.05; decreased libido 23% versus 0, p<0.05; hair loss 20% versus 6%; abdominal pain 20% versus 6%; acne 11% versus 0; breast tenderness 8% versus 3%; nausea 0 versus 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 versus 45% (SE 7%) At 12 months 34% (SE 5%) 32% (SE 7%)		Mean age of girls at delivery was 17.8 ± 1.4 years. 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% versus 44%; sexual inactivity 21% versus 13%, forgetting an injection/pill 13% versus 50%. DMPA users injection site pain (5%), OC users no refills (13%)		Median duration of use was 8.1 months DMPA versus 5.4 months OC.

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 Pregnancy (cumulative)	100% DMPA versus 93% OC continuers, and 75% versus 79% discontinuers would recommend the method to their friend. 44% versus 73% discontinuers would used the methods again. 11% DMPA (SE 3%) versus 28% (SE 7%) OC, p=0.003.		
Heber 1988 [433]	Case-series	3	627	Women from an Australian general practice who had used DMPA	DMPA	-	14,242 cycles	Pregnancy Reasons for discontinuation (n=500)	1 in total (her DMPA was given 7 weeks postpartum) 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.	Not stated	Age range of women was 15 to 51 years

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 [263] 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 versus OC discontinuers) Menstrual pattern	45% versus 73%, p=0.002 Nausea 0 versus 17%, disrupted menstrual cycles 40% versus 4%, forgot to take 0 versus 25%, multiple side effects 40% versus 25%, planning pregnancy 0 versus 8%, not sexually active 0 versus 13%, couldn't attend clinic 8% versus 0, weight gain 12% versus 0, ran our 0 versus 8% Normal 20.5% DMPA versus 50% OC, irregular 38% versus 23%, too frequent 6% versus 4%, prolonged 15% versus 9%, amenorrhoea 20.5% versus 14%.	Not stated	Pregnancy also reported in 13 adolescents, all of whom had discontinued contraception before becoming pregnant (3% DMPA versus 24% OC, RR for pregnancy with OC versus DMPA 9.09 (95% CI 2.1 to 39.2). Mean time to pregnancy was 17.1 (SE 0.4) versus 13.2 (SE 1.18) months with DMPA versus OC, p<0.001.
Colli 1999 [262] 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.

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 versus 9.5 versus 13.1; preference 10.2, 4.7, 11.5; contraception not required 5.8 versus 1.6 versus 5.1; vasectomy 2.5 versus 2.6 versus 3.6; sterilization 2.9 versus 1.6 versus 2.1; weight problem 5.7 versus 0.1 versus 2.5; menorrhagia 1.5 versus 4.4 versus 1.8; noncompliance 2.1 versus 0.1 versus 4.2; intermenstrual bleeding 1.1 versus 1.0 versus 4.7; pelvic pain 0.4 versus 4.4 versus 0.9; headaches 0.6 versus 0.1 versus 3.8; pelvic infections 0.1 versus 3.4 versus 0.1; pregnancy whilst using method 0.3 versus 2.2 versus 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 [264] 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 versus 8.2±1.0 months.	Satisfaction	48% versus 52% "somewhat", 29% versus 35% dissatisfied, 73% versus 61% would recommend to a friend, 51% versus 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% versus 68% irregular bleeding, 40% versus 42% weight gain, 26% versus 35% increased headaches, 20% versus 42% mood changes, 20% versus 29% fatigue, 14% versus 19% breast tenderness, 14% versus 16% amenorrhoea, 20% versus 10% loss of scalp hair, 6% versus 19% painful administration site, 9% versus 10% acne.		Norplant removal rates 23% during year 1, 29% year 2, 48% year 3.
								Menstrual pattern after discontinuation	50% versus 81% resumed in first month, duration of bleeding 7.0±2.0 versus 5.0±2.5 days		Between-group differences in return of menses, and conception rate significant, p=0.01.

								BMI STI	Gains of 1.1±0.3 versus 1.3±0.6 from baseline during mean 9.2±0.9 versus 21.8±1.6 months of use 20% versus 64% during use, 20% versus 32% after discontinuation		

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 Abnormal Pap smears (atypia & squamous intraepithelial lesions) Pregnancy	28% versus 3% during use, 32% versus 20% after discontinuation 26% versus 45% during use, 6% versus 10% after discontinuation 20% versus 48% during follow-up		
Harel 1995 [434] 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 Reasons for continued DMPA use	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%) Total population: not having to take pill every day (54%), easier than previous method (16%), no periods (15%)	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%).

								Satisfaction	52% versus 39% versus 87% very, 78% versus 84% versus 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% versus 19% versus 20%		
								Reasons for discontinuation	Most common: irregular bleeding (25%), weight gain (11%), amenorrhoea (8%), increased appetite (8%)		
								BMI	Gains of 1.08±0.29 versus 1.28±0.49 versus 1.05±0.73 from baseline at 6 months		
								Pregnancy	0		

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 [267] 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 versus 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.

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% versus 26%, p<0.05 (irregular bleeding 5% versus 19%, amenorrhoea 0 versus 2%, 'other' 0.5% versus 5%) Missing injection 0.5% versus 4%, p<0.05, personal reasons 4% versus 9%, lost to follow-up 0 versus 9%, protocol violation 1% versus 0%.		Centres that gave structured counselling were separated from those that gave routine counselling by the Yangtze river.

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 [55] 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 versus 43.4% routine, p<0.05 Amenorrhoea 3% versus 17% p<0.05, irregular bleeding 3% versus 10% p<0.05, heavy bleeding 2% versus 5% p<0.05, weight gain 2% versus 2%, vomiting 1% versus 1%, dizziness 0.6% versus 0.6%, depression 1% versus 2%, loss of libido 1% versus 2%, planned pregnancy 1% versus 2%, lost to follow-up 1% versus 2%.	None stated	DMPA administered within the first five days of the menstrual cycle. Method of randomisation not reported.

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.							

Chapter 6 – 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 [266] 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 versus 3 injection intervals for DMPA versus NET-EN)	Mean duration of bleeding Incidence of prolonged bleeding (>21 days)	35.9 (SD 31.55) versus 33.2 (SD 20.58) days 21% versus 25.5% in the first injection interval; 12.7% versus 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 versus 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 [265] 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 versus 76% oestrone versus 74% placebo (p<0.001 ethinylestradiol versus 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 versus 9 versus 9 days 2 versus 2 versus 3 days		non-steroidal anti-inflammatory agents (n=4), iron, calcium, vitamins, and/or diazepam (n=14). Their outcomes were not reported separately.

Chapter 6 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 [313] 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 versus DMPA: 76.5% versus 70.2% at 1 year (RR 1.09, 95% CI 0.86 to 1.39) 90.2% versus 89.4% at 2 years (RR 1.01, 95% CI 0.88 to 1.15)	Not stated	
Garza-Flores 1985 [311] 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 versus 2.6 ± 1.7 months NET-EN, p<0.001	WHO	Mean duration of use 2.9 ± 1.2 years DMPA versus 3.2 ± 1.6 years NET-EN (minimum 1.2 years both 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
Pardthaisong 1980 [312] 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 versus 4.5 months IUD. 78.2% ± 1.5 versus 79.0% ± 4.4 at 1 year 92.1% ± 1.1 versus 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 versus 27.7 ± 5.1 years IUD; mean number of pregnancies 1.5 ± 1.4 versus 2.0 ± 1.6; proportions never pregnant were 4.4% versus 0 ($p<0.05$ for all differences between groups). Duration of DMPA or IUD use not reported.

Chapter 6 Progestogen only injectable contraceptives: weight changes

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[435] 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 versus 1.4 kg at 1 year, and 7.2 versus 1.8 kg at 2 years in the interval groups (n=219), and gain of 3.2 versus 0.6 kg at 1 year, and 6.5 versus 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.

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[268]	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 versus 3.1 versus 3.4 kg in overweight (BMI > 8th percentile for their age) DMPA users versus 'normal' weight DMPA users versus overweight OC users in 1 study. Similar weight gain in overweight (>91 kg) DMPA users versus total group of DMPA users in 1 study (mean 2.0 versus 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[436] 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 versus baseline of 1.7 versus 2.2 versus 2.3 kg in OC versus DMPA versus NET-EN at 6 months Systolic: mean increases of 5.2 versus 4.5 versus 4.5 mmHg; Diastolic: mean increases of 2.2 versus 4.1 versus 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 6 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[269] 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 versus 18% nonusers at baseline; 21% DMPA users versus 36% in DMPA discontinuers versus 14% nonusers at month 6; 21% versus 22% versus 14% at month 12; 16% versus 19% versus 15% at month 18; 21% versus 28% versus 16% at month 24; 18% versus 25% versus 14% at month 30; 8% versus 21% versus 12% at month 36. OR 1.44; 95%CI 1.00 to 2.07 in continuous DMPA users versus 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 versus 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.

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 versus 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% versus 17%).		
Gupta 2001[270] 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) versus +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.

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 versus -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 versus +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 versus 6.3 control, p<0.03)

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 [272] 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 versus 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.

Chapter 6 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 [275] 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[92] 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 POICs 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.

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)		

Chapter 6 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[278]	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 versus 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

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 [301] 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.

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 [279] 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 breastfeeding or recently breastfeeding, 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).

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[280] 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 breastfeeding or recently breastfeeding, not recently pregnant, and not had hysterectomy or	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 versus 0.469±0.042 COC versus 0.473±0.048 nonusers (p=NS between groups)	Not stated	Same inclusion criteria and endpoint as Petitti 2000[279]

				oophorectomy.							

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 versus 0.393±0.042 versus 0.392±0.051 (p=NS between groups)		Mean duration of COC use was significantly greater than of DMPA use (68 months versus 42). BMD measured by single X-ray absorptiometry.
Bahamondes 1999 [281] 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 breastfeeding 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 versus 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).						

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 [300] 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.		

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 [289] 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 versus 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 versus 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 versus 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 versus 0.71 ± 0.01 Between-group difference not reported		
								Trochanter (g/cm^2)	0.75 ± 0.01 versus 0.74 ± 0.02 Between-group difference -0.012 (95% CI -0.047 to 0.023)		

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 [288] 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 versus 0.48 in both groups (95% CI -0.02 to 0.02) Ultradistal: 0.38 ± 0.06 versus 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 versus 147.51 ± 91.9 (95% CI -122 to -68.1)		
Lara-Torre 2004 [297] 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%,	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 versus control.

									+5.89% (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 versus 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 [298] 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 versus +2.46% Norplant versus +1.52% COC versus +2.85% control at 1 year. In the 15 girls followed up for 2 years, changes in BMD were -3.12% DMPA versus +9.33% Norplant	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.

									versus +9.49% 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**
									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 versus other groups. Norplant users reported significantly more aerobic exercise than other groups.
Scholes 2004 [290]	Cross sectional	3	174	Girls aged 14 to 18 years using DMPA. Exclusions: pregnancy, breastfeeding, cancer in past 10 years, other	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 versus 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

				conditions known to affect bone density, taking steroids or other medications known to affect bone metabolism.				Total hip BMD (mean [SD] g/cm^2)	0.940 (0.013) versus 0.970 (0.013), p=NS		women. BMD measured using dual X-ray absorptiometry. 17 (18%) of the comparison group were using a OC.

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) versus 0.992 (0.012), p=NS		Significantly more DMPA users were smokers (36% versus 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 [286] USA	Cross-sectional	3	457	Women aged 18 to 39 years who were new or prevalent DMPA users. Exclusions: pregnancy, breastfeeding, 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 versus 1.044 ± 0.007, p=0.03	Not stated	The results presented are baseline data from a prospective cohort study.[291] 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
				(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 versus 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 versus 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 versus 1.091 ± 0.005, p=NS		In those aged 18 to 21 years (48 DMPA users versus 62 nonusers), BMD significantly lower in DMPA users at all sites measured p<0.01.

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 [291] USA	Cohort	2+	457	Women aged 18 to 39 years who were new or prevalent DMPA users. Exclusions: pregnancy, breastfeeding, 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.[286] 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).

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.[286]

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 [287] 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 versus age-matched normal values (Z score)	-0.332 (95% CI -0.510 to -0.154) p<0.001 versus '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 versus age-matched normal values (Z score)	-0.088 (95% CI -0.237 to +0.060) p=0.25 versus '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.		

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 [299] 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, breastfeeding, 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 versus control, and norethindrone COC versus control p=0.01. DMPA versus 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 versus DMPA or 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
Merki-Feld 2003 [292] 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, breastfeeding, 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 [296] 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 breastfeeding.	DMPA (n=30)	OC (n=30)	-	BMD at distal forearm (g/cm^2)	0.566±0.043 DMPA versus 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 versus 0.423±0.048 OC (p=NS)		
Wanichsetakul 2002 [295] 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 versus 1.065±0.121 COC versus 1.096±0.116 nonusers (DMPA versus 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 versus 0.933±0.120 versus 0.894±0.109		
								Ward's triangle BMD	0.833±0.137 versus 0.849±0.152 versus 0.794±0.154		

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 versus 0.790±0.105 versus 0.759±0.089 0.44±0.056 versus 0.44±0.067 versus 0.429±0.062 0.621±0.058 versus 0.616±0.084 versus 0.597±0.075		
Cundy 1998 [285] 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 versus 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.

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 [283] 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 versus 1.03 control, p=0.001	Not stated	BMD measured by dual X-ray absorptiometry. Mean age of DMPA group 42.8 years versus 40 control (range 34 to 46). Median duration of DMPA use 6 years (range 5 to 15).
								Femoral neck BMD	0.69 versus 0.83, p=0.001		
								Trochanter BMD	0.59 versus 0.71, p=0.001		
								Ward's triangle BMD	0.58 versus 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 [284] 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 versus 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 versus 1.04, p=0.01		
								Trochanter BMD	0.78 versus 0.84, p<0.002		
								Ward's triangle BMD	0.90 versus 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 6 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 [302]	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 6 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 [327] 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% versus 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% versus 45%, relative risk 0.94, 95%CI 0.71 to 1.25		

Chapter 6 Progestogen only injectable contraceptives: breastfeeding

Bibliographic reference	Study Type	Evidence level	Number of patients	Patients characteristics	Interventions	Comparison	Length of follow-up	Outcomes measures	Effect size	Source of funding	Additional comments
Halderman 2002[318] 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	Breastfeeding continuation rate	74.1% DMPA versus 72.1% hormonal users versus 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 versus 29.4 years), had lower gravidity and parity, and less experience with prior breastfeeding (46% versus 62%).
								Breastfeeding status	Exclusively; 36.5% versus 36% versus 34.8% With bottle supplementation; 63.5% versus 64% versus 65.2% Not breastfeeding (bottle only) due to insufficient milk 27.3% versus 34.9% versus 50%		

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 [319] USA	Cohort	2+	103	Women who had delivered a healthy neonate, were breastfeeding 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	Breastfeeding continuation rate	37% versus 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 versus 25 years), and fewer were married (12% versus 29%).
								Duration of breastfeeding (median)	10.14 weeks (95% CI 0.71 to 19.57) versus 6.57 (95% CI 3.43 to 9.71)		
								First introduction of formula feed (median)	15 versus 14 days		

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 [317] Iran	Cohort	2-	140	Women who were exclusively breastfeeding, 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 7 Progestogen only subdermal implants

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 [332] Multicentred: Thailand Indonesia Europe Chile/Hungary Canada Finland Sweden Singapore UK USA China Associated references: [40;329;333-342;368;372;437;438]	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

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 Menstrual disturbances at 2 years Dysmenorrhoea Weight changes Mood changes/libido Skin effects	None in either group Amenorrhoea: 21.7% versus 4.7% Infrequent bleeding: 27.3% versus 21.1% Frequent bleeding: 6.1% versus 3.4% Prolonged bleeding: 12.1% versus 9.0% Implanon Improvement: 35% Exacerbation: 3.4% Norplant: Overall improvement to a lesser extent (no data) Increase of > 10% from baseline: 8.7% in both groups Emotional lability: 4.9% versus 7.6% Decreased libido: 3.3% versus 5.4% Acne: 18.5% versus 21.2%		

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
								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% versus 20.1% 6% versus 7.9% 0.3% versus 0% 0.2% versus 4.8% Pain: 0.9 % versus 1.9% Ovulation at 3 months: 93.6% versus 90.9%		
PMSN 2001 [163] [344] Multicentre: Chile Columbia Egypt Sri Lanka Thailand Indonesia	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	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

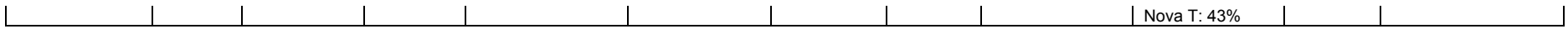
Bangladesh China									At 3 years Norplant: 0.53 Copper IUD: 3.04		

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%		

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		

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
									4.16 to 6.20)		
								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		

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
									0.93 to 3.40)		
								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[345] 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%		Use Norplant data only


Nova T: 43%

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 [298] 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 [41] 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:	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 [439] 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 [346] 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	

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%		

Chapter 7 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 [357] 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 [358] 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 [359] 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 [360] 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 [362] 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 7 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 [365] 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 [282] 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 [279] included in the review reported a decreased BMD among Norplant users	MRC, WHO	Studies reviewed were of poor quality

Chapter 7 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 [332]	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 [440] 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

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 [373] 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 [374] 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	

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 [375] 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% versus 53% headaches: 26% versus 42% Emotional problems: 26% versus 5% amenorrhoea: 6% versus 0% (Both groups gained weight at 12 months: 4 kg versus 2 kg)	Not stated	
Harel 1996 [264] 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% versus 68% Weight gain: 40% versus 42% Increased headaches: 26% versus 35% Mood changes: 20% versus 42% Fatigue: 20% versus 29% Amenorrhoea: 14% versus 16% Loss of hair: 20% versus 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 [376] 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% versus 37% versus 10% Mood swings: 54% versus 32% versus 25% acne: 30% versus 12% versus 10% hair loss: 15% versus 0% versus 0% weight gain: 52% versus 40% versus 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[377] 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 [298] 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

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 [378] 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 [379] 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 [380] 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	

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 [315] 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 [383] 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 [213] 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 [441] 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 [236] 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 7 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 [370] 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 versus 22.4 days ± 7.3	Not stated	

Chapter 7 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 [442] 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 [351] 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% Mean no of bleeding days: Mefenamic: 11.6 ± 8.2 Placebo:17.2 ± 10.2	Universit y funding	2 patients dropped out from placebo group

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 [352] 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% versus 14% versus 50% Mean no of bleeding days: 2.6 ± 1.4 versus 5.4 ± 5.1 versus 12.3 ± 5.4	Not stated	
Witjaksono 1996 [353] 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 [443] 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 versus 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 [354] 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 [444] 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 [356] 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 8 Economic evaluation

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Sonnenberg et al, 2004 USA [384]	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	

Study	Population Study method	Intervention Details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Trussell et al, 1997 USA [385]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Koenig et al, 1996 USA [386]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Trussell et al, 1995 USA [387]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Ortemeier et al, 1994 USA [388]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Chiou et al, 2003 USA [389]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Ashraf et al, 1994 USA [390]	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 [391]	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	

Study	Population Study method	Intervention Details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Janowitz et al, 1994 Thailand [392]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Phillips 2000 UK [393]	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 subdermal implant Norplant, and progestogen only intrauterine 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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
McGuire et al, 1995 UK [394]	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.	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
Hughes et al, 1996 UK [395]	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	

Study	Population Study method	Intervention details	Costs Outcomes	Results	Comments	Study Type	Evidence level
French et al, 2000 UK [109]	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 versus IUD>250mm^3 at 1 year: £168 Norplant versus IUD>250mm^3 at 2 years: £166 Norplant versus IUD≤250mm^3: £162 Norplant versus OC (perfect use/low cost): £173 Norplant versus OC (perfect use/high cost): £142 Norplant versus OC (imperfect use/low cost): £167 Norplant versus OC (imperfect use/high cost): £135 Norplant versus DMPA: £161 Mirena versus IUD>250mm^3 at 1 year: £89 Mirena versus IUD>250mm^3 at 2 years: £84 Mirena versus IUD>250mm^3 at 3 years: £80 Mirena versus IUD>250mm^3 at 5 years: £84 Mirena versus IUD≤250mm^3 at 1 year: £82 Mirena versus IUD≤250mm^3 at 3 years: £39 Pregnancies averted=additional risk of pregnancy with option(2) compared with option(1): Norplant versus IUD>250mm^3 at 1 year: 0.00066 (Norplant is more effective) Norplant versus IUD>250mm^3 at 2 years: 0.00315 Norplant versus IUD≤250mm^3: 0.00718 Norplant versus OC (perfect use): 0.00166 Norplant versus OC (imperfect use): 0.00830 Norplant versus DMPA: 0.00000 Mirena versus IUD>250mm^3 at 1 year: -0.00003 (IUD is more effective) Mirena versus IUD>250mm^3 at 2 years: 0.00490 Mirena versus IUD>250mm^3 at 3 years: 0.00890 Mirena versus IUD>250mm^3 at 5 years: 0.00476 Mirena versus IUD≤250mm^3 at 1 year: 0.00704 Mirena versus IUD≤250mm^3 at 3 years: 0.05301	Incremental costs per pregnancy averted: Norplant versus IUD>250mm^3 at 1 year: £255,102 Norplant versus IUD>250mm^3 at 2 years: £52,692 Norplant versus IUD≤250mm^3: £22,566 Norplant versus OC (perfect use/low cost): £104,198 Norplant versus OC (perfect use/high cost): £85,258 Norplant versus OC (imperfect use/low cost): £20,073 Norplant versus OC (imperfect use/high cost): £16,285 Norplant versus DMPA: DMPA dominates (less costly, equally effective) Mirena versus IUD>250mm^3 at 1 year: IUD dominates Mirena versus IUD>250mm^3 at 2 years: £17,205 Mirena versus IUD>250mm^3 at 3 years: £9,042 Mirena versus IUD>250mm^3 at 5 years: £17,739 Mirena versus IUD≤250mm^3 at 1 year: £11,684 Mirena versus 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	

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