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Heavy Menstrual Bleeding

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National Collaborating Centre for

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Women's and Children's Health

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1 **Stakeholder organisations**

- 2 ▪ Action and Support Group for Medical Victims of Richard Neale
- 3 ▪ Addenbrooke's NHS Trust
- 4 ▪ Airedale General Hospital
- 5 ▪ Anglesey Local Health Board
- 6 ▪ Association for Continence Advice (ACA)
- 7 ▪ Association for Improvements in the Maternity Services
- 8 ▪ Association of British Health-Care Industries
- 9 ▪ Association of the British Pharmaceuticals Industry (ABPI)
- 10 ▪ AstraZeneca UK Ltd
- 11 ▪ Barnsley Primary Care Trust
- 12 ▪ Barts and The London NHS Trust
- 13 ▪ Bedfordshire & Hertfordshire NHS Strategic Health Authority
- 14 ▪ Biocompatibles UK Ltd
- 15 ▪ Biosphere Medical Europe
- 16 ▪ Birmingham Heartlands & Solihull NHS Trust
- 17 ▪ Boston Scientific Limited
- 18 ▪ British Association for Counselling and Psychotherapy
- 19 ▪ British Menopause Society
- 20 ▪ British National Formulary (BNF)
- 21 ▪ British Psychological Society, The
- 22 ▪ British Society of Gynaecological Endoscopy
- 23 ▪ British Society of Interventional Radiology
- 24 ▪ Buckinghamshire Hospitals NHS Trust
- 25 ▪ Campaign Against Hysterectomy (CAH)

- 1 ▪ CASPE
- 2 ▪ Change People
- 3 ▪ Chartered Society of Physiotherapy
- 4 ▪ CIS'ters
- 5 ▪ City Hospitals Sunderland NHS Trust
- 6 ▪ Commission for Social Care Inspection
- 7 ▪ Connecting for Health
- 8 ▪ Conwy & Denbighshire NHS Trust
- 9 ▪ Cytoc UK Limited
- 10 ▪ Denbighshire Local Health Board
- 11 ▪ Department of Health
- 12 ▪ Dudley Group of Hospitals NHS Trust
- 13 ▪ ECLIPSE Trial Management Group, University of Birmingham Clinical
- 14 Trials Unit
- 15 ▪ Endometriosis SHE Trust (UK)
- 16 ▪ Faculty of Family Planning and Reproductive Health Care
- 17 ▪ FEmISA
- 18 ▪ Fibroid Network Charity
- 19 ▪ Gloucestershire Hospitals NHS Trust
- 20 ▪ Good Hope NHS Trust
- 21 ▪ Gorlin Syndrome Group
- 22 ▪ Greater Peterborough Primary Care Partnership-North PCT
- 23 ▪ Guerbet Laboratories Ltd
- 24 ▪ Healthcare Commission
- 25 ▪ Hospital Infection Society

- 1 ▪ Johnson & Johnson Medical
- 2 ▪ L'Arche UK
- 3 ▪ Leeds Teaching Hospitals NHS Trust
- 4 ▪ Liverpool Women's Hospital NHS Trust
- 5 ▪ Luton and Dunstable Hospital NHS Trust
- 6 ▪ Maidstone and Tunbridge Wells NHS Trust
- 7 ▪ Maternity Health Links
- 8 ▪ Medicines and Healthcare Products Regulatory Agency (MHRA)
- 9 ▪ Mental Health Foundation
- 10 ▪ Microsulis Medical Limited
- 11 ▪ Mid Staffordshire General Hospitals NHS Trust
- 12 ▪ National Council for Disabled People, Black, Minority and Ethnic
- 13 Community (Equalities)
- 14 ▪ National Endometriosis Society
- 15 ▪ National Osteoporosis Society
- 16 ▪ National Patient Safety Agency
- 17 ▪ National Public Health Service – Wales
- 18 ▪ NHS Direct
- 19 ▪ NHS Health and Social Care Information Centre
- 20 ▪ NHS Modernisation Agency, The
- 21 ▪ NHS Purchasing & Supply Agency
- 22 ▪ NHS Quality Improvement Scotland
- 23 ▪ Newcastle PCT
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- 25 ▪ North Tees and Hartlepool NHS Trust

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- 2 ▪ Oxford Radcliffe Hospitals NHS Trust
- 3 ▪ Pfizer Limited
- 4 ▪ Princess Alexandra Hospital NHS Trust
- 5 ▪ Queen Mary's NHS Trust
- 6 ▪ Regional Public Health Group - London
- 7 ▪ Rotherham Primary Care Trust
- 8 ▪ Royal College of General Practitioners
- 9 ▪ Royal College of General Practitioners Wales
- 10 ▪ Royal College of Nursing (RCN)
- 11 ▪ Royal College of Obstetricians & Gynaecologists
- 12 ▪ Royal College of Pathologists
- 13 ▪ Royal College of Physicians of London
- 14 ▪ Royal College of Psychiatrists
- 15 ▪ Royal Shrewsbury Hospital NHS Trust
- 16 ▪ Royal Surrey County Hospital
- 17 ▪ Schering Health Care Ltd
- 18 ▪ Scottish Intercollegiate Guidelines Network (SIGN)
- 19 ▪ Sheffield South West Primary Care Trust
- 20 ▪ Sheffield Teaching Hospitals NHS Trust
- 21 ▪ Society & College of Radiographers
- 22 ▪ Society for Academic Primary Care
- 23 ▪ Society of Consultants and Lead Clinicians in Reproductive Health
- 24 ▪ South East Sheffield Primary Care Trust
- 25 ▪ Staffordshire Moorlands Primary Care Trust

- 1 ▪ Tameside and Glossop Acute Services NHS Trust
- 2 ▪ The Daisy Network
- 3 ▪ The David Lewis Centre
- 4 ▪ The Haemophilia Society
- 5 ▪ The Hysterectomy Association
- 6 ▪ The London Fibroid Clinic
- 7 ▪ The National Association of Assistants in Surgical Practice
- 8 ▪ The North West London Hospitals NHS Trust
- 9 ▪ The Royal Society of Medicine
- 10 ▪ The Royal West Sussex Trust
- 11 ▪ UK Anaemia
- 12 ▪ University College Londons Hospital NHS Trust
- 13 ▪ University Hospital Birmingham NHS Trust
- 14 ▪ Vitaline Pharmaceuticals UK Ltd
- 15 ▪ Welsh Assembly Government (formerly National Assembly for Wales)
- 16 ▪ Wirral Hospital NHS Trust
- 17 ▪ Women's Health
- 18 ▪ Women's Health Concern
- 19 ▪ Wyeth Laboratories
- 20

1 Abbreviations

Abbreviation	
AUB	Abnormal Uterine Bleeding
CI	Confidence interval
COC	Combined Oral Contraceptives
DUB	Dysfunctional Uterine Bleeding
EL	Evidence level (level of evidence)
FSH	Follicle Stimulating Hormone
GDG	Guideline Development Group
GPP	Good practice point
HMB	Heavy Menstrual Bleeding
LH	Luteinising Hormone
MBL	Menstrual Blood Loss
MEA	Microwave Endometrial Ablation
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
PBAC	Pictorial Blood loss Assessment Chart
PPIP	Patient and Public Involvement Programme
QALYS	Quality adjusted life years
QoL	Quality of Life
RCT	Randomised controlled trial
REA	Rollerball Endometrial Ablation
RR	Relative risk
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
TBEA	Thermal Balloon Endometrial Ablation
TCRE	Transcervical Resection of the Endometrium
vWD	Von Willebrand's Disease
WMD	Weighted mean difference

1 Glossary of terms

Abnormal Uterine Bleeding	Abnormal bleeding can occur when the menstrual period is not regular, when bleeding lasts longer than normal, is heavier than normal, or when bleeding patterns change.
Anovulatory	An anovulatory cycle is a menstrual cycle in which ovulation fails to occur.
Applicability	The extent to which the results of a study or review can be applied to the target population for a clinical guideline.
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 actually doesn't. Bias can occur by chance or as a result of <i>systematic</i> errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see <i>Selection bias</i> , <i>Performance bias</i> , <i>Information bias</i> , <i>Confounding</i> , <i>Publication bias</i> .
Bilateral Salpingo-Oophorectomy	Surgical removal of the ovaries and fallopian tubes
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 <i>bias</i> . See also <i>Double blind study</i> ,

	<i>Single blind study, Triple blind study.</i>
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 (<i>control</i>) group of patients.
Case-control study	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called <i>retrospective</i> as they look back in time from the outcome to the possible causes.
Causal relationship	Describes the relationship between <i>two variables</i> whenever it can be established that one causes the other. For example there is a causal relationship between a treatment and a disease if it can be shown that the treatment changes the course or outcome of the disease. Usually <i>randomised controlled trials</i> are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association between two variables. For example, if it happened that everyone who had eaten a particular food became sick, and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food

caused the sickness – unless all other possible causes (e.g. environmental factors) had been ruled out.

CCT

See *Controlled clinical trial*.

Clinical audit

A *systematic* process for setting and monitoring standards of clinical care. Whereas ‘guidelines’ define what the best clinical practice should be, ‘audit’ investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.

Clinical effectiveness

The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical ‘effectiveness’ is not the same as *efficacy*.

Clinical governance

A framework through which NHS organisations are accountable for both continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.

Clinical impact

The effect that a guideline recommendation is likely to have on the treatment, or treatment outcomes, of the target population.

Clinical importance

The importance of a particular guideline

recommendation to the clinical management of the target population.

Clinical question	This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a <i>focused question</i> .
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 <i>controlled clinical trials</i> and <i>randomised controlled trials</i> .
Clinician	A health care professional providing patient care, e.g. doctor, nurse, physiotherapist.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called <i>randomised controlled trials</i> . The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the <i>Cochrane Library</i> .
Cognitive training	Method of mental training used to improve physical control of the body.
Cohort	A group of people sharing some common characteristic (e.g. 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, e.g. comparing mortality between one group that received a specific treatment and one group which 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.

Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
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 are 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 we are 95% confident that the true effect lies.

**Confounder or
confounding factor**

Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.

**Consensus
development
conference**

A technique used for the purpose of reaching an agreement on a particular issue. It involves bringing together a group of about 10 people who are presented with evidence by various interest groups or experts who are not part of the decision making group. The group then retires to consider the questions in the light of the evidence presented and attempts to reach a consensus. See also *Consensus methods*.

Consensus methods

A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include *Delphi* and *nominal group* techniques, and *consensus development conferences*. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a

	particular topic.
Consistency	The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also <i>Homogeneity</i> .
Control Event Rate	See <i>Event rate</i> .
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 (CCT)	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 CCT where patients are randomly allocated to treatment and comparison groups is called a <i>randomised controlled trial</i> .
Cost benefit analysis	A type of <i>economic evaluation</i> where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost effectiveness	Value for money. A specific health care treatment is said to be 'cost-effective' if it gives a greater health gain than could be achieved by using the resources in other ways.
Cost effectiveness	A type of <i>economic evaluation</i> comparing the costs

analysis	and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.
Cost utility analysis	A special form of <i>cost effectiveness analysis</i> where health effects are measured in <i>quality adjusted life years</i> . A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.
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 <i>longitudinal study</i> which follows a set of people over a period of time.)
Data set	A list of required information relating to a specific disease.
Decision analysis	Decision analysis is the study of how people make decisions or how they <i>should</i> make decisions. There are several methods that decision analysts use to help people to make better decisions, including

	<i>decision trees.</i>
Decision tree	A decision tree is a method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or overall cost-effectiveness of different actions can then be compared.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity e.g. if their position or department is funded by a pharmaceutical company.
Delphi method	A technique used for the purpose of reaching an agreement on a particular issue, without the participants meeting or interacting directly. It involves sending participants a series of postal questionnaires asking them to record their views. After the first questionnaire, participants are asked to give further views in the light of the group feedback. The judgements of the participants are statistically aggregated, sometimes after weighting for expertise. See also <i>Consensus methods</i> .
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.
Dominance	A term used in health economics describing when an option for treatment is both less clinically effective and more costly than an alternative option. The less effective and more costly option is said to be 'dominated'.

Double blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Dysfunctional Uterine Bleeding	abnormal vaginal bleeding that occurs during a menstrual cycle that produced no egg (ovulation did not take place). Occurrence of irregular or excessive uterine bleeding in the absence of pregnancy, infection, trauma, new growth or hormone treatment.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In <i>health economic</i> evaluations the consequences should include health outcomes.
EER	Experimental Event Rate – see <i>Event rate</i> .
Effectiveness	See <i>Clinical effectiveness</i> .
Efficacy	The extent to which a specific treatment or intervention, under <u>ideally controlled conditions</u> (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care.
Elective	Name for clinical procedures that are regarded as advantageous to the patient but not urgent.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.
Endometrium	The endometrium is the inner membrane in the uterus
Epidemiology	Study of diseases within a population, covering the causes and means of prevention.
Event rate	The proportion of patients in a group for whom a specified health event or outcome is observed. Thus, if out of 100 patients, the event is observed in 27, the event rate is 0.27 or 27%. Control Event

	Rate (CER) and Experimental Event Rate (EER) are the terms used in <i>control</i> and experimental groups of patients respectively.
Evidence based	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Evidence based clinical practice	Evidence based clinical practice involves making decisions about the care of individual women 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 evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria	See <i>Selection criteria</i> .
External validity	The degree to which the results of a study hold true in non-study situations, e.g. in routine clinical practice. May also be referred to as the <i>generalisability</i> of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Focus group	A <i>qualitative research</i> technique. It is a method of group interview or discussion of between 6–12 people focused around a particular issue or topic. The method explicitly includes and uses the group interaction to generate data.

Focused question	A study question that clearly identifies all aspects of the topic that are to be considered while seeking an answer. Questions are normally expected to identify the patients or population involved, the treatment or intervention to be investigated, what outcomes are to be considered, and any comparisons that are to be made. E.g. Do insulin pumps (intervention) improve blood sugar control (outcome) in adolescents with type 1 diabetes (population) compared with multiple insulin injections (comparison)? See also <i>Clinical question</i> .
Forest plot	A graphical display of results from individual studies on a common scale, allowing visual comparison of results and examination of the degree of <i>heterogeneity</i> between studies.
Funnel plot	Funnel plots are simple scatter plots on a graph. They show the treatment effects estimated from separate studies on the horizontal axis against a measure of sample size on the vertical axis. <i>Publication bias</i> may lead to asymmetry in funnel plots.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also <i>External validity</i> .
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Good practice point	Recommended good practice based on the expert experience of the guideline development group (and possibly incorporating the expertise of a wider reference group). A guideline development group may produce a 'Good practice point' (rather than an evidence based recommendation) on an important

	topic when there is a lack of research evidence.
Grade of recommendation	A code (e.g. A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision-making about appropriate health care for specific clinical conditions.
Guideline recommendation	Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.
Health economics	A branch of economics which studies decisions about the use and distribution of health care resources.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.
Health Technology Appraisal (HTA)	A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost effectiveness of a <i>health technology</i> . NICE health technology appraisals are designed to provide patients, clinicians and managers with an authoritative source of advice on new and existing

	health technologies.
Heterogeneity	Or lack of <i>homogeneity</i> . The term is used in <i>meta-analyses</i> and <i>systematic reviews</i> 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 the patient populations, outcome measures, definition of <i>variables</i> or duration of follow-up.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well conducted study. Well-conducted <i>randomised controlled trials</i> (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	This means that the results of studies included in a <i>systematic review</i> or <i>meta analysis</i> are similar and there is no evidence of <i>heterogeneity</i> . Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also <i>Consistency</i> .
HTA	See <i>Health Technology Appraisal</i> .
Hysterectomy	Surgical removal of the uterus
Hysteroscopy	A hysteroscopy is an examination of the inside of the womb (uterus) using a hysteroscope. Hysteroscopy allows for direct visualisation of the inside of the womb. The hysteroscope is carefully passed through

the vagina and cervix, and into the womb. During the procedure a biopsy may be taken for examination.

In depth interview	A <i>qualitative research</i> technique. It is a face to face conversation between a researcher and a respondent with the purpose of exploring issues or topics in detail. Does not use pre-set questions, but is shaped by a defined set of topics or issues.
Inclusion criteria	See <i>Selection criteria</i> .
Information bias	Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of <i>blinding</i>), response errors (e.g. lack of <i>blinding</i> if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).
Intention to treat analysis	An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of clinical effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.
Internal validity	Refers to the integrity of the study design.
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.
Interventional procedure	A procedure used for diagnosis or treatment that involves making a cut or hole in the patient's body, entry into a body cavity or using electromagnetic radiation (including X-rays or lasers). The National

	Institute for Clinical Excellence (NICE) has the task of producing guidance about whether specific interventional procedures are safe enough and work well enough for routine use.
leiomyomas	See uterine fibroids
Level of evidence	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the <i>hierarchy of evidence</i> and how well it has adhered to recognised research principles.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a <i>cross sectional study</i> which observes a defined set of people at a single point in time.)
Masking	See <i>Blinding</i> .
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 e.g. 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 <i>Systematic review & Heterogeneity</i> .
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Methodology	The overall approach of a research project, e.g. the study will be a <i>randomised controlled trial</i> , of 200 people, over one year.
Microwave	MEA System is a surgical device that uses

Endometrial Ablation	microwave energy to treat excessive menstrual bleeding by destroying tissue lining the uterus (womb). A long slender tube that delivers microwave energy is inserted into the uterus to destroy tissue.
	The MEA technique uses microwaves (at a fixed frequency of 9.2 GHz) to destroy the uterine glandular lining, using a hand-held applicator (microwave probe) that is inserted into the uterine cavity.
Multicentre study	A study where subjects were selected from different locations or populations, e.g. a co-operative study between different hospitals; an international collaboration involving patients from more than one country.
Myometrium	The muscular outer layer of the uterus
Non-systematic review	See <i>Review</i> .
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.
Observation	Observation is a research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research.
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 (e.g. whether or not people received a specific treatment or intervention) are studied in relation to

changes or differences in other(s) (e.g. 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 1 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*, *Risk ratio*.

Off label

Treatment used outside of license rather than unlicensed use

Oophorectomy

Surgical removal of one or both ovaries

Outcome

The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Ovulatory

Ovulation is the release of a single, mature egg from the ovarian follicle.

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 $P=0.03$. What this means is that if there really was no difference between treatments then 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 (i.e. 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*.

PCT

See *Primary Care Trust*.

**Pictorial Blood
Assessment Chart**

A chart for recording level of menstrual loss based on appearance of sanitary pads. On the basis of the chart results the total amount of menstrual blood loss can be estimated.

Pilot study

A small scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full scale study begins.

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 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 <i>placebo</i> itself.
Power	See <i>Statistical power</i> .
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.
Probability	How likely an event is to occur, e.g. how likely a treatment or intervention will alleviate a symptom.
Prognostic factor	Patient or disease characteristics, e.g. age or <i>co-morbidity</i> , which influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in <i>variables</i> (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these prognostic factors become <i>confounding factors</i> . See also <i>Prognostic marker</i> .
Prognostic marker	A <i>prognostic factor</i> used to assign patients to categories for a specified purpose – e.g. for treatment, or as part of a clinical trial, according to the likely progression of the disease. For example, the purpose of randomisation in a clinical trial is to produce similar treatment groups with respect to important <i>prognostic factors</i> . This can often be achieved more efficiently if randomisation takes place within subgroups defined by the most

important prognostic factors. Thus if age was very much related to patient outcome then separate randomisation schemes would be used for different age groups. This process is known as stratified random allocation.

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*.

Protocol A plan or set of steps which defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.

Publication bias Studies with statistically significant results are more likely to get published than those with non-significant results. *Meta-analyses* that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a *funnel plot*.

Qualitative research Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. 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.
Quality adjusted life years (QALYS)	A measure of health outcome which looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to one year of life in perfect health, or two years at 50% health, and so on.
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.
Quasi experimental study	<p>A study designed to test if a treatment or intervention has an effect on the course or outcome of disease. It differs from a <i>controlled clinical trial</i> and a <i>randomised controlled trial</i> in that:</p> <p>a) the assignment of patients to treatment and comparison groups is not done randomly, or patients are not given equal probabilities of selection, or b) the investigator does not have full control over the allocation and/or timing of the intervention, but nonetheless conducts the study as if it were an experiment, allocating subjects to treatment and comparison groups.</p>
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 <i>cluster randomisation</i>) being

**Randomised
controlled trial**

entered into a study has the same chance of receiving each of the possible interventions.

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 (e.g. an adverse reaction to the drug being tested) in one group of subjects compared to another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 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/ past and does not involve studying future events. This contrasts with studies that are <i>prospective</i> .
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
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 <i>relative risk</i> is sometimes used as a synonym of risk ratio.
Rollerball Endometrial Ablation	REA destroys the inner layers of the uterus using a electrically heated 'rollerball'.
Royal Colleges	In the UK medical/nursing world the term royal colleges, as for example in 'The Royal College of.....', refers to organisations which usually combine an educational standards and examination role with the promotion of professional standards.
Saline-infused sonography	Saline infusion sonography is a minimally invasive ultrasound technique used in women to view the inside of the uterus. Sterile saline is injected into the endometrial cavity through a small catheter while a transvaginal ultrasound is performed. This allows real-time imaging of the uterus as the saline is put inside. The saline fills and distends (expands) the endometrial cavity, providing visualization of the anatomic structures within.

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.
Sampling	Refers to the way participants are selected for inclusion in a study.
Sampling frame	A list or register of names which is used to recruit participants to a study.
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN was established in 1993 to sponsor and support the development of evidence-based clinical guidelines for the NHS in Scotland.
Secondary care	Care provided in hospitals.
Selection bias	Selection bias has occurred if: the characteristics of the <i>sample differ</i> from those of the wider population from which the sample has been drawn OR there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to 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.
Semi-structured interview	Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
Sensitivity	In diagnostic testing, it refers to the chance of having a positive test result given that you have the

disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a ‘false positive’. The sensitivity of a test is also related to its ‘negative predictive value’ (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To fully judge the accuracy of a test, its *Specificity* must also be considered.

SF-36

The SF-36 Health Survey was developed for the Medical Outcomes Study, and has been tested and validated extensively. The SF-36 includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone.¹

SIGN

See *Scottish Intercollegiate Guidelines Network*

Single blind study

A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.

Specific indication

When a drug or a device has a specific remit to treat

a specific condition and is not licensed for use in treating other conditions or diseases.

Specificity

In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a ‘false negative’. The specificity of a test is also related to its ‘positive predictive value’ (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its *Sensitivity* must also be considered.

Standard deviation

A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.

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 (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 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*.

Structured interview

A research technique where the interviewer controls the interview by adhering strictly to a questionnaire

	or interview schedule with pre-set questions.
Study checklist	A list of questions addressing the key aspects of the research methodology that must be in place if a study is to be accepted as valid. A different checklist is required for each study type. These checklists are used to ensure a degree of consistency in the way that studies are evaluated.
Study population	People who have been identified as the subjects of a study.
Study quality	See <i>Methodological quality</i> .
Study type	The kind of design used for a study. <i>Randomised controlled trial, case-control study, cohort study</i> are all examples of study types.
Subject	A person who takes part in an experiment or research study.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic	Methodical, according to plan; not random.
Systematic error	Refers to the various errors or biases inherent in a study. See also <i>Bias</i> .
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 <i>meta-analysis</i> .
Systemic	Involving the whole body.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study – e.g. in terms of age, disease state, social background.
Tertiary centre	A major medical centre providing complex

treatments which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also *Primary care* and *Secondary care*.

**Thermal Balloon
Endometrial
Ablation**

TBEA destroys the inner layers of the uterus by transferring heat from heated liquid within a balloon inserted into the uterine cavity. TBEA cannot be used on women with large or irregular uterine cavities because the balloon must be in direct contact with the uterine wall to cause ablation.

**Trans-Cervical
Resection of the
Endometrium**

The uterus is distended with fluid at constant pressure to permit resectoscopic visualisation of the target area. Under video surveillance, a small wire electrocautery loop is used to excise the basal layer of the endometrium

**Transvaginal
ultrasound**

Transvaginal ultrasound is a method of imaging the genital tract in women. The ultrasound machine sends out high-frequency sound waves, which bounce off body structures to create a picture on a screen.

With the transvaginal technique, the ultrasound transducer (a hand-held probe) is inserted directly into the vagina. It is therefore closer to pelvic structures than with the conventional transabdominal technique (with the probe on the skin of the abdomen).

Trust

A trust is an NHS organisation responsible for providing a group of healthcare services. An *acute trust* provides hospital services. A *mental health trust* provides most mental health services. A *primary care trust* buys hospital care on behalf of the local population, as well as being responsible for the

	provision of community health services.
Uterine fibroid	smooth muscle tumours of the uterus, generally benign although occasionally (<1%) malignant. They vary tremendously in size from millimetres to tens of centimetres, and are associated with heavy periods, pressure symptoms and occasionally pain. They are responsive to the female hormones oestrogen and progesterone, generally shrinking to a degree at the menopause.
Uterus	The uterus (womb) is a hollow, pear-shaped organ located in a woman's lower abdomen between the bladder and the rectum. The narrow, lower portion of the uterus is the cervix; the broader, upper part is the corpus. The corpus is made up of two layers of tissue (myometrium and endometrium)
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also <i>External validity, Internal validity</i> .
Variable	A measurement that can vary within a study, e.g. 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 which can be assessed or measured.

1
2
3

1 Introduction

Heavy Menstrual Bleeding has an adverse effect on the quality of life of many women. It is not a problem associated with significant mortality and consequently, it is thought by some doctors to be unimportant. However, many women seek help from their general practitioners and it is a common reason for referral into secondary care.

In order for women to be successfully treated, it is essential that the underlying problem is understood by both the patient and the doctor. The guideline provides this background information as well as covering epidemiology, physiology, investigation and ultimately, treatment. The aim is to consider the evidence and review it, taking into account, both the patient and the doctor's viewpoint. This is not always easy but it is anticipated that the information contained in the guideline will help patients reach an informed and sensible decision with their doctors. Having read the guideline they will know what questions to ask and the options available to them. As a result of constructive dialogue, we hope that patients will be able to trust the advice given by their practitioner since they will be confident that they have the latest information and are able to use it to inform this decision making process.

Clinical guidelines have been defined as systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions. The guideline has been developed with the aim of providing guidance on heavy menstrual bleeding. The effectiveness of

1 the different treatments as well as their risks and benefits are discussed in
2 relation to their use in the treatment of HMB but the discussion cannot be
3 extrapolated to the use of particular treatments to relieve other symptoms e.g.
4 hysterectomy for cancer or endometriosis. The implications of each treatment
5 in relation to fertility are also clearly stated in order that no woman has a
6 treatment that renders her infertile unless this is her specific wish.

7

8 Uterine fibroids are a common cause of heavy menstrual bleeding. The
9 diagnosis and management are discussed in some depth although treatment
10 for symptoms other than heavy menstrual bleeding are not included. The
11 most up to date information is discussed in order that the guideline will reflect
12 current best practice. There are other gynaecological conditions such as
13 adenomyosis or endometriosis where menorrhagia maybe associated with
14 other menstrual symptoms as part of the presenting complaint. These
15 conditions are excluded because heavy menstrual bleeding is not usually the
16 principal presenting complaint and also, endometriosis could be the topic of a
17 separate guideline. It is not possible to cover every condition but some of the
18 advice centred in this guideline will be relevant in some circumstances.

19

20 In the early 1990's, it was estimated that at least 60% of women presenting
21 with heavy menstrual bleeding would have a hysterectomy to treat the
22 problem, often as a first line. However, things have changed and the number
23 of hysterectomies is decreasing rapidly. This is a major operation associated
24 with significant complications in a minority of cases and also, it is an emotive
25 procedure, the concept of which is despised by certain sections of society.

1 However, it is also associated with a very high satisfaction rate by those who
2 have had one. The number of hysterectomies, the apparent lack of pathology,
3 and the lack of discussion of alternatives was a major cause for concern by
4 the profession as well as the public. One of the principle aims of our guideline
5 is to consider hysterectomy as well as the other treatment options and
6 determine when they are likely to be the most appropriate for any particular
7 individual..

8

9 Alternative effective treatments are available for women who have a normal
10 uterus and no significant pathology such as large uterine fibroids. The
11 consequence of this is that the hysterectomies that are performed, tend to be
12 more complicated than many of those in the past. This has significant
13 implications for the acquisition and maintenance of surgical skills and this area
14 is covered in some depth in the guideline. Surgical competence is an
15 extremely important issue and recommendations are included as to how this
16 might be made apparent to a patient. One possibility suggested is that details
17 of the surgical practice of individual gynaecologists should be in the public
18 domain.

19

20 It is often very difficult for patients to appreciate that not all women are
21 suitable for a particular new 'non-invasive' procedure. Often, the media will
22 discuss new therapies and give patients hope that can in some instances, be
23 inappropriate. This guideline aims to avoid this by including sensible and
24 comprehensible discussions so that women can understand why doctors
25 advise for or against particular treatment. Doctor's decisions are informed by

1 experience as well as their knowledge of the evidence base. It is important
2 that both happen together facilitating an open discussion with the patient to
3 allow the doctor's view to be put into context. If the opinion of the doctor is
4 contrary to that of the patient then a second opinion should be sought. This
5 will mean that patients will get the best possible advice and treatment that will
6 lead to resolution of their HMB.

7

8 **1.2 Aim of the guideline**

9 Clinical guidelines have been defined as 'systematically developed statements
10 which assist clinicians and patients in making decisions about appropriate
11 treatment for specific conditions'.² The following areas are covered in this
12 guideline:

- 13 a) The guideline will provide advice on patient educational interventions
14 and information provision to improve patient satisfaction.
- 15 b) The guideline will provide advice on diagnosis of women presenting
16 with HMB, including guidance on appropriate investigations and referral, and
17 the cost-effectiveness of undertaking such investigations.
- 18 c) The guideline will provide advice on the medical management of HMB,
19 including short and long-term outcomes, adverse events, cost-effectiveness
20 and subsequent treatment.
- 21 d) The guideline will provide advice on the indications for referral to
22 secondary care management.
- 23 e) The guideline will provide advice to determine if, and when, surgical
24 procedures are most appropriate.

f) The guideline will provide advice on operative procedures used for endometrial ablation/resection in HMB, including short and long-term outcomes, cost-effectiveness, adverse events, and subsequent treatment.

g) The guideline will provide advice on operative procedures used for uterine artery embolisation in HMB, including short and long-term outcomes, cost-effectiveness, adverse events, and subsequent treatment.

h) The guideline will provide advice on operative procedures and other techniques used for hysterectomy and myomectomy in HMB, including short and long-term outcomes, adverse events, and subsequent treatment. This will include guidance on minimal access techniques (laparoscopically).

i) When hysterectomy is the most appropriate option, issues relating to the removal of healthy ovaries will be examined.

j) The competencies required by practitioners who wish to carry out surgical techniques and other interventions, such as UAE will be provided.

k) Advice on treatment options will be based on the best evidence available to the Guideline Development Group. When referring to pharmacological interventions, the guideline will normally recommend use within the licensed indications. Exceptionally, and only where the evidence clearly supports it, the guideline may recommend use of a pharmacological intervention beyond its licensed indications. The guideline recommendations will assume that prescribers will use the Summary of Product Characteristics for prescribing decisions for individual women. The guideline recommendations will be based on the assessment of short and long-term outcomes and complications for all treatments.

1.3 Areas outside of the remit of the guideline

The guideline will not address the following issues:

- Conditions where heavy menstrual bleeding is not the main presenting menstrual symptom. An example is endometriosis, which is often dysmenorrhoea associated with pelvic pain. Such conditions will not be covered even if there is concurrent menorrhagia.
- Issues relating to anaesthetics in surgery.
- Issues relating to fertility will only be examined as they relate to treatment for HMB but not as a separate issue.
- Women with heavy bleeding receiving exogenous steroids (e.g. hormone replacement therapy).
- Gynaecological bleeding problems (other than HMB).

1.4 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales, in particular:

- General practitioners, Gynaecologists, Gynaecological nurse specialists and Interventional radiologists.
- Those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners and public health and trust managers
- The guideline will also be of use to women with HMB.

A version of this guideline for women, their families and the public is available, entitled <Insert IFP Title>. It can be downloaded from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/insertcorrectaddress) or ordered via the NHS Response Line (0870 1555 455) quoting reference number <Insert Reference Number>.

1.5 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 Consumer/patient representatives
- Two General Practitioners
- One Interventional radiologist
- One Epidemiologist
- One Nurse-specialist
- Four Gynaecologist surgeons

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

All GDG members' interests were recorded on declaration form provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry.

1.6 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including:

- NICE guideline. Osteoporosis: assessment of fracture risk and prevention of osteoporotic fracture in individuals at high risk. [Under development]
- NICE guideline. Referral guidelines for suspected cancer. 2005. CG26
- NICE guideline. Long-acting Reversible Contraception. 2005. CG030.
- Technology Appraisal. Fluid-filled thermal balloon and microwave endometrial ablation techniques for heavy menstrual bleeding. 2004. No. 78.
- Technology Appraisal: The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women (expected publication date September 2005).
- Technology Appraisal on secondary prevention of osteoporotic fractures in post menopausal women (this is awaiting a response following appeal).
- Technology Appraisal on strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis.

- 1 ▪ Interventional Procedure Guidance. Impedance-controlled bipolar
2 radiofrequency ablation for menorrhagia (expected publication date
3 2004).
- 4 ▪ Interventional Procedure Guidance. Laparoscopic hysterectomy
5 (expected publication date February 2005).
- 6 ▪ Interventional Procedure Guidance. Free fluid thermal endometrial
7 ablation. 2004. No. 51.
- 8 ▪ Interventional Procedure Guidance. Laparoscopic laser myomectomy.
9 2003. No. 23.
- 10 ▪ Interventional Procedure Guidance. Hysteroscopic laser myomectomy
11 (In development).
- 12 ▪ Interventional Procedure Guidance. Photodynamic endometrial
13 ablation. 2004. No. 47.
- 14 ▪ Interventional Procedure Guidance. Microwave endometrial ablation.
15 2004. No. 7.
- 16 ▪ Interventional Procedure Guidance. Balloon thermal endometrial
17 ablation. 2003. No. 6.
- 18 ▪ Interventional Procedure Guidance. Uterine artery embolisation for
19 fibroids. 2004. No. 94.

20 **1.7 Guideline Development Methodology**

21 This guideline was commissioned by NICE and developed in accordance with
22 the guideline development process outlined in the NICE Technical Manual.³
23
24

1 **Literature search strategy**

2 Initial scoping searches were executed to identify relevant guidelines (local,
3 national and international) produced by other development groups. The
4 reference lists in these guidelines were checked against subsequent searches
5 to identify missing evidence.

6

7 Relevant published evidence to inform the guideline development process and
8 answer the clinical questions was identified by systematic search strategies.
9 Additionally, stakeholder organisations were invited to submit evidence for
10 consideration by the GDG provided it was relevant to the clinical questions,
11 and of equivalent or better quality than evidence identified by the search
12 strategies.

13

14 Systematic searches to answer the clinical questions formulated and agreed
15 by the GDG were executed using the following databases via the OVID
16 platform: Medline (1966 onwards), Embase (1980 onwards), Cumulative Index
17 to Nursing and Allied Health Literature (1982 onwards), British Nursing Index
18 (1985 onwards), PsycINFO (1967 onwards), Cochrane Central Register of
19 Controlled Trials (2nd Quarter 2006), Cochrane Database of Systematic
20 Review (1st Quarter 2006) and Database of Abstracts of Reviews of Effects
21 (1st Quarter 2006).

22

23 Search strategies combined relevant controlled vocabulary and natural
24 language in an effort to balance sensitivity and specificity. Unless advised by
25 the GDG, searches were not date specific. Language restrictions were not

1 applied to searches. Both generic and specially developed methodological
2 search filters were used appropriately.

3
4 Searches to identify economic studies were undertaken using the above
5 databases, and the NHS Economic Evaluations Database (NHS EED)
6 produced by the Centre for Reviews and Dissemination at the University of
7 York.

8
9 There was no systematic attempt to search grey literature (conferences,
10 abstracts, theses and unpublished trials). Hand searching of journals not
11 indexed on the databases was not undertaken.

12
13 At the end of the guideline development process, searches were updated and
14 re-executed, thereby including evidence published and included in the
15 databases up to June 2006. Any evidence published after this date was not
16 included. This date should be considered the starting point for searching for
17 new evidence for future updates to this guideline.

18
19 Further details of the search strategies, including the methodological filters
20 employed, can be obtained from the NCC-WCH.

21 22 **Synthesis of clinical effectiveness evidence**

23 Evidence relating to clinical effectiveness was reviewed using established
24 guides³⁻¹⁰ and classified using the established hierarchical system shown in

1 Table 1.1.¹⁰ This system reflects the susceptibility to bias that is inherent in
 2 particular study designs.

3

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

13 **Table 1.1** - Levels of evidence for intervention studies

Level	Source of evidence
1++	<ul style="list-style-type: none"> High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	<ul style="list-style-type: none"> Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	<ul style="list-style-type: none"> Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	<ul style="list-style-type: none"> 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+	<ul style="list-style-type: none"> 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-	<ul style="list-style-type: none"> 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

1
2 For each clinical question, the highest available level of evidence was
3 selected. Where appropriate, for example, if a systematic review, meta-
4 analysis or RCT existed in relation to a question, studies of a weaker design
5 were not included. Where systematic reviews, meta-analyses and RCTs did
6 not exist, other appropriate experimental or observational studies were
7 sought. For diagnostic tests, test evaluation studies examining the
8 performance of the test were used if the efficacy of the test was required, but
9 where an evaluation of the effectiveness of the test in the clinical management
10 of patients and the outcome of disease was required, evidence from RCTs or
11 cohort studies was used.

12
13 The system described above covers studies of treatment effectiveness.
14 However, it is less appropriate for studies reporting diagnostic tests of
15 accuracy. In the absence of a validated ranking system for this type of test,
16 NICE has developed a hierarchy for evidence of accuracy of diagnostic tests
17 that takes into account the various factors likely to affect the validity of these
18 studies (Table 1.2).³

1

2 **Table 1.2** - Levels of evidence for studies of the accuracy of diagnostics tests

Level	Type of evidence
Ia	Systematic review (with homogeneity)* of level-1 studies [†]
Ib	Level-1 studies [†]
II	Level-2 studies [‡]
	Systematic reviews of level-2 studies
III	Level-3 studies [§]
	Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[†]Level-1 studies are studies:

that use a blind comparison of the test with a validated reference standard (gold standard)
in a sample of patients that reflects the population to whom the test would apply.

[‡]Level-2 studies are studies that have only one of the following:

narrow population (the sample does not reflect the population to whom the test would apply)
use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
the comparison between the test and reference standard is not blind
case-control studies

[§]Level-3 studies are studies that have at least two or three of the features listed above

3

1 For economic evaluations, no standard system of grading the quality of
2 evidence exists. Economic evaluations that are included in the review have
3 been assessed using a quality assessment checklist based on good practice
4 in decision- analytic modelling.¹¹

5
6 Evidence was synthesised qualitatively by summarising the content of
7 identified papers in evidence tables and agreeing brief statements that
8 accurately reflected the evidence. Quantitative synthesis (meta-analysis) was
9 performed where appropriate.

10
11 Summary results and data are presented in the guideline text. More detailed
12 results and data are presented in the accompanying evidence tables. Where
13 possible, dichotomous outcomes are presented as relative risks (RRs) with
14 95% confidence intervals (CIs) and continuous outcomes are presented as
15 mean differences with 95% CIs or standard deviations (SDs). Meta-analyses
16 based on dichotomous outcomes are presented as pooled odds ratios (ORs)
17 with 95% CIs and meta-analyses based on continuous outcomes are
18 presented as weighted mean differences (WMDs) with 95% CIs.

20 **Health economics**

21 The aim of the economic input into the guideline was to inform the GDG of
22 potential economic issues relating to HMB. The health economist helped the
23 GDG by identifying topics within the guideline that might benefit from
24 economic analysis, reviewing the available economic evidence and where
25 necessary, conducting (or commissioning) economic analysis. Reviews of

published health economic evidence are presented alongside the reviews of clinical evidence and are incorporated within the relevant evidence statement and recommendations. For some questions, no published evidence was identified, and decision analytic modelling was undertaken. Results of this modelling are presented in Appendix A.

Economic evaluations in this guideline have been conducted in the form of a cost-effectiveness analysis, with the health effects measured in an appropriate non-monetary outcome indicator. The NICE technology appraisal programme measures outcomes in terms of quality adjusted life years (QALYs). Where possible, this approach has been used in the development of this guideline. However, where it has not been possible to estimate QALYs gained as a result of an intervention, an alternative measure of effectiveness has been used.

Cost-effectiveness analysis, with the units of effectiveness expressed in QALYs (known as cost-utility analysis), is widely recognised as a useful approach for measuring and comparing the efficiency of different health interventions. The QALY is a measure of a health outcome which assigns to each period of time (generally one year) a weight, ranging from 0 to 1, corresponding to health related quality of life during that period. It is one of the most commonly used outcome measures in health economics. A score of one corresponds to full health and a score of zero corresponds to a health state equivalent to death. Negative valuations, implying a health state worse than death, are possible. Health outcomes using this method are measured

by the number of years of life in a given health state, multiplied by the value of being in that health state.

Forming and grading recommendations

For each clinical question, recommendations were derived using, and explicitly linked to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree evidence statements and recommendations. Shortly before the consultation period, formal consensus methods were used to agree guideline recommendations (modified Delphi technique) and to select 5–10 key priorities for implementation (nominal group technique).

Each recommendation was graded according to the level of evidence upon which it was based using the established system shown in Table 1.3.⁹ For issues of therapy or treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) equates to a grade A recommendation. For issues of prognosis, the best possible level of evidence (a cohort study) equates 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.

In addition, the GDG made research recommendations for areas where it was believed that research was needed.

1 **Table 1.3** - Classification of recommendations ⁹

Class	Evidence
A	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Evidence level 3 or 4, or ▪ Extrapolated evidence from studies rated as 2+, or ▪ Formal consensus
D(GPP)	<ul style="list-style-type: none"> ▪ A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

2

3

4 **External review**

5 This guideline has been developed in accordance with the NICE guideline
6 development process. This has included giving registered stakeholder
7 organisations the opportunity to comment on the scope of the guideline at the
8 initial stage of development and on the evidence and recommendations at the

1 concluding stage. The developers have carefully considered all of the
2 comments during the consultation by registered stakeholders and validation
3 by NICE.

4

5 **Outcome measures used in the guideline**

6 At the start of the guideline development process the GDG outlined a list of
7 primary outcomes:

8 Change in menstrual blood loss (MBL)

9 Complications or adverse events associated with treatments

10 Change in quality of life measures (QoL)

11

12 **1.8 Schedule for updating the guideline**

13 Clinical guidelines commissioned by NICE are published with a review date 4
14 years from date of publication. Reviewing may begin earlier than 4 years if
15 significant evidence that affects guideline recommendations is identified
16 sooner. The updated guideline will be available within 2 years of the start of
17 the review process.

2 Summary of recommendations and practice algorithm

2.1 Key priorities for implementation (key recommendations)

For clinical purposes, HMB is defined as excessive menstrual blood loss leading to interference with the physical, emotional, social and material quality-of-life of a woman, and which can occur alone or in combination with other symptoms. **[D]**

Ultrasound should be considered the first line diagnostic tool for the identification of structural pathology in HMB. **[A]**

An endometrial biopsy should be taken if the woman has persistent intermenstrual bleeding, is aged 45 years and over and has declined or failed adequate medical treatment, and before undertaking surgical or UAE. **[D(GPP)]**

Patients referred to secondary care with menorrhagia should be provided with an information pack prior to their outpatient appointment. **[A]**

Patients should be allowed choice of treatment, but within the clinicians' remit of balancing risk and benefits based on evidence and their competence. **[D(GPP)]**

When pharmaceutical treatment is felt to be necessary and hormonal treatment is acceptable to a woman with HMB, then the order in which interventions should be considered is:

- First line, LNG-IUSⁱ **[A]**
- Second line, tranexamic acid **[A]** or NSAIDs **[A]** or COCs ⁱⁱ **[B]**
- Other treatment options for consideration are: Norethisterone (15mg) daily from days 5 to 26 of the cycle or Injected long acting progestogens.ⁱⁱⁱ

When pharmaceutical treatment is felt to be necessary and hormonal treatment is not acceptable (for example, if a woman is wishing to conceive) to women with HMB then the order in which treatments should be considered is:

- First line, tranexamic acid **[A]**,
- Second line, NSAIDs. **[A]**

ⁱ World Health Organisation Medical Eligibility Criteria for Contraceptive Use (WHOMEC) criteria apply. These involve the assessment of the individuals' suitability for contraceptives, based on their specific profile of potential benefits and harms. This allows informed decision-making by the woman prior to the start of treatment.¹²

ⁱⁱ World Health Organisation Medical Eligibility Criteria for Contraceptive Use (WHOMEC) criteria apply. These involve the assessment of the individuals' suitability for contraceptives, based on their specific profile of potential benefits and harms. This allows informed decision-making by the woman prior to the start of treatment.¹³

ⁱⁱⁱ Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of injected progestogen is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

Hysterectomy should not be used as a first line treatment solely for HMB, unless in the presence of large fibroids, or other symptoms. **[D(GPP)]**

In women with HMB alone, with uterus no bigger than a ten week pregnancy, endometrial ablation methods should be considered preferable to hysterectomy.^{iv v} **[A]**

The route of hysterectomy to be used should be considered in the following order: first line, vaginal; second line, abdominal; and third line, laparoscopic. **[A]**

2.2 Summary of recommendations

Chapter 3 - Defining HMB

For clinical purposes, HMB is defined as excessive menstrual blood loss leading to interference with the physical, emotional, social and material quality-of-life of a woman, and which can occur alone or in combination with other symptoms. **[D]**

Chapter 3.8.2

HMB should be recognised as having a major impact on a woman's quality of life.

[C] Chapter 3.8.2

^{iv} Reference should be made to the manufacturers own limits on uterus size.

^v It is recommended that the Medicines and Healthcare products Regulatory Agency (MHRA), safety notices on endometrial ablation should be followed (MDA [1998] SN 9812 Devices used for endometrial ablation achieved by thermal means, and MDA [1999] SN 1999(18) Devices used for endometrial ablation).

When deciding care options, clinicians should take into account the range and natural variability in menstrual cycles and blood loss in an individual woman and within normal populations. **[D(GPP)] Chapter 3.8.2**

A successful treatment outcome is determined by the woman with HMB. **[D(GPP)] Chapter 3.8.2**

Uses of direct or non-direct measurement techniques for MBL are not routinely recommended in women presenting with HMB. **[D(GPP)] Chapter 3.8.2**

Chapter 4 Investigations for HMB

History taking for HMB

History taking should cover: the nature of bleeding problem; symptoms suggesting potentially serious pathology; and other factors that will determine treatment options. **[D(GPP)] Chapter 4.2.4**

If history taking reveals HMB without the presence of pathology, then there is no need to undertake a physical examination prior to initiating first-line medical treatment. **[D (GPP)] Chapter 4.2.4**

If history taking suggests pathology with symptoms such as inter-menstrual or post coital bleeding, pelvic pain and/or pressure symptoms then physical examination and/or appropriate investigations should be undertaken to make a diagnosis. **[D (GPP)] Chapter 4.2.4**

Physical examination

Physical examination should be undertaken prior to investigations (except haematological investigations). **[D (GPP)] Chapter 4.3.4**

Laboratory tests in HMB

A full blood count should be undertaken on women with suspected HMB. **[C]**

Chapter 4.4.4

A serum ferritin test should not routinely be undertaken in women with HMB. **[B]**

Chapter 4.4.4

Female hormone testing for women with HMB should not be performed. **[C] Chapter**

4.4.4

Thyroid testing in women with HMB should only be undertaken where other symptoms of thyroid disease are present. **[C] Chapter 4.4.4**

Testing for coagulation disorders should only routinely be undertaken on women with HMB in their teenage years or who have had HMB since menarche, and have other personal or family history suggesting a coagulation disorder. **[C] Chapter 4.4.4**

Investigations for structural and histological abnormalities

Ultrasound should be considered the first line diagnostic tool for the identification of structural pathology in HMB. **[A] Chapter 4.5.4**

Hysteroscopy with biopsy is an accurate method for identification of endometrial and some submucosal pathology, but should be considered only where ultrasound outcomes are inconclusive. **[A] Chapter 4.5.4**

An endometrial biopsy should be taken if the woman has persistent intermenstrual bleeding, is aged 45 years and over and has declined or failed adequate medical treatment, and before undertaking surgical or UAE. **[D(GPP)] Chapter 4.5.4**

Saline Infusion Sonography should not be undertaken as a first-line investigation of HMB. **[A] Chapter 4.5.4**

MRI scanning should not be used as a first line diagnostic tool for HMB. **[B] Chapter 4.5.4**

D&C should not be used as a diagnostic tool for HMB. **[B] Chapter 4.5.4**

If a woman has fibroids that are intracavitary or a uterine length greater than 12cm then referral for specialist opinion should be offered. **[D(GPP)]**

Chapter 4.5.4

Chapter 5 Education, Information Provision, Patient Choice and Lifestyle Interventions

Patient education, information provision and counselling & Patient Choice

Patients referred to secondary care with menorrhagia should be provided with an information pack prior to their outpatient appointment. **[A] Chapter 5.4.4**

Where a potential treatment involves the loss of fertility then counselling and support should be made available to the woman throughout the care pathway. **[D(GPP)]**

Chapter 5.4.4

A woman with HMB should be given the opportunity to review and veto any treatment decision. **[D(GPP)] Chapter 5.4.4**

Patients should be allowed choice of treatment, but within the clinicians' remit of balancing risk and benefits based on evidence and their competence. **[D(GPP)]**

Chapter 5.4.4

A woman with HMB must have the option of gaining a second medical opinion where a clinician has no knowledge or opinions are at odds. **[D(GPP)] Chapter 5.4.4**

A woman with HMB should have adequate time and support in the decision making process, especially where the treatment decision has irreversible results. **[D(GPP)]**

Chapter 5.4.4

Where a potential treatment involves the loss of fertility then counselling and support should be made available to the woman throughout the care pathway. **[D(GPP)]**

Chapter 5.4.4

Chapter 6 & 7 Hormonal & Non-hormonal medical treatments for HMB

When pharmaceutical treatment is felt to be necessary and hormonal treatment is acceptable to a woman with HMB, then the order in which interventions should be considered is:

- First line, LNG-IUS^{vi} **[A]**
- Second line, tranexamic acid **[A]** or NSAIDs **[A]** or COCs ^{vii} **[B]**
- Other treatment options for consideration are: Norethisterone (15mg) daily from days 5 to 26 of the cycle or Injected long acting progestogens. ^{viii} **[A]**

Chapter 7.4.4

When pharmaceutical treatment is felt to be necessary and hormonal treatment is not acceptable (for example, if a woman is wishing to conceive) to women with HMB then the order in which treatments should be considered is:

First line, tranexamic acid **[A]**,

Second line, NSAIDs. **[A]** Chapter 7.4.4

^{vi} World Health Organisation Medical Eligibility Criteria for Contraceptive Use (WHOMEC) criteria apply. These involve the assessment of the individuals' suitability for contraceptives, based on their specific profile of potential benefits and harms. This allows informed decision-making by the woman prior to the start of treatment. ¹⁴

^{vii} World Health Organisation Medical Eligibility Criteria for Contraceptive Use (WHOMEC) criteria apply. These involve the assessment of the individuals' suitability for contraceptives, based on their specific profile of potential benefits and harms. This allows informed decision-making by the woman prior to the start of treatment. ¹⁵

^{viii} Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of injected progestogen is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

1
2 Use of NSAIDs or tranexamic acid should be stopped if they do not improve
3 symptoms within 3 months. **[D(GPP)] Chapter 7.4.4**

4
5 Ongoing use of NSAIDs and tranexamic acid can be recommended for as long as
6 they are found to be beneficial by women with HMB. **[D(GPP)] Chapter 7.4.4**

7
8 When HMB coexists with dysmenorrhoea then NSAIDs should be preferred to
9 tranexamic acid. **[D(GPP)] Chapter 7.4.4**

10
11 A second medical treatment should be considered when a first-line medical
12 treatment has failed for women with HMB. **[D] Chapter 7.4.4**

13
14 Women should be fully counselled regarding the changes to the bleeding pattern
15 particularly in the first few months post-insertion of an LNG-IUS. Perseverance for at
16 least 6-months is recommended for benefits to be appreciated. **[D (GPP)] Chapter**
17 **7.4.4**

18
19 Oral progestogens given during the luteal phase only should not be used to treat
20 women with HMB. **[A] Chapter 7.4.4**

21
22 Danazol is not recommended for routine use in the treatment of HMB. **[A] Chapter**
23 **7.4.4**

GnRH-a could be considered when all other management options, including surgery or UAE, are contraindicated for the treatment of a woman. If it is to be used for more than 6 months then 'Add-Back' therapy is recommended.^{ix} **[B] Chapter 7.4.4**

Etamsylate should not be used in the treatment of HMB. **[A] Chapter 7.4.4**

Chapter 8 Indications for non-hysterectomy surgery

Surgery (excluding hysterectomy) should be considered in cases of HMB where bleeding is: having a severe impact on a woman's quality of life, and the woman has completed her family (except in the case of UAE or myomectomy where fertility is potentially retained). **[C] Chapter 8.2.4**

Women should be made aware of the impact on fertility that surgery will have in all cases. **[D(GPP)] Chapter 8.2.4**

Endometrial ablation should be considered in women who have a normal uterus and small uterine fibroids (< 3cm). **[A] Chapter 8.2.4**

For women with large fibroids in presence of HMB, and other significant symptoms (dysmenorrhoea; pressure symptoms), referral for consideration of surgery or UAE as a first line can be recommended. **[D(GPP)] Chapter 8.2.4**

^{ix} Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of GnRH-a is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

Chapter 9 Surgery as first treatment for HMB

Endometrial ablation may be offered to women with HMB as an initial treatment in secondary care after full discussion of outcomes and other treatment options. **[A]**

Chapter 9.2.4

Hysterectomy should not be used as a first line treatment solely for HMB, unless in the presence of large fibroids, or other symptoms. **[D(GPP)] Chapter 9.2.4**

Chapter 10 Non-hysterectomy surgery for HMB

Dilation and Curettage

D&C should not be used as a therapeutic treatment for HMB. **[C] Chapter 10.2.4**

Endometrial ablation / resection

Hysteroscopy should be undertaken post-dilation, pre-procedure when undertaking endometrial ablation. **[D(GPP)] Chapter 10.4.5**

Endometrial ablation should not be undertaken on women wishing to become pregnant at any time in the future. **[D(GPP)] Chapter 10.4.5**

Second generation ablation techniques (MEA, TBEA) should be considered ahead of first generation techniques (TCRE, REA). **[A] Chapter 10.4.5**

If a TBEA is being undertaken then endometrial thinning is not required. **[D(GPP)]**

Chapter 10.4.5

If an MEA is being undertaken then scheduling of surgery for post-menstrual phase is an alternative to endometrial thinning. **[A] Chapter 10.4.5**

In women with HMB alone, with uterus no bigger than a ten week pregnancy, endometrial ablation methods should be considered preferable to hysterectomy. ^{x xi} **[A]**

Chapter 10.4.5

Women must be counselled on the need to use effective contraception after endometrial ablation. **[D(GPP)] Chapter 10.4.5**

Ablative techniques should be undertaken under local anaesthetic where appropriate **[D(GPP)] Chapter 10.4.5**

Chapter 11 Interventions for Uterine Fibroids

Prior to scheduling of UAE or myomectomy, the uterus and fibroid(s) should be assessed by imaging, preferably MRI when available. **[D (GPP)] Chapter 11.7**

UAE is recommended for women with HMB associated with uterine fibroids and who want to retain their uterus and/or avoid surgery. **[B] Chapter 11.7**

^x Reference should be made to the manufacturers own limits on uterus size.

^{xi} It is recommended that the Medicines and Healthcare products Regulatory Agency (MHRA), safety notices on endometrial ablation should be followed (MDA [1998] SN 9812 Devices used for endometrial ablation achieved by thermal means, and MDA [1999] SN 1999(18) Devices used for endometrial ablation).

Use of GnRH-a should be stopped as soon as UAE has been scheduled. **[D (GPP)]**

Chapter 11.7

Myomectomy is recommended for women with HMB associated with uterine fibroids and who want to retain their uterus. **[D] Chapter 11.7**

Women should be informed that UAE or myomectomy will potentially allow them to retain their fertility. **[C] Chapter 11.7**

Chapter 12 Hysterectomy

Hysterectomy should be considered only where:

- Other treatment options have failed or are inappropriate,
- Women have completed their families,
- There is a wish for amenorrhoea,
- And either women (who have been fully counselled) request it or other forms of further treatment are contraindicated. **[C] Chapter 12.3.4**

The route of hysterectomy to be used should be considered in the following order: first line, vaginal; second line, abdominal; and third line, laparoscopic. **[A] Chapter 12.3.4**

Individual patient assessment is essential when deciding route of hysterectomy.

Factors that need to be taken into account are:

- presence of other gynaecological conditions or disease,
- uterine size,
- presence and size of uterine fibroids,
- mobility and descent of uterus,
- size and shape of vagina,
- and history of previous surgery. **[D(GPP)] Chapter 12.3.4**

Any counselling should include: psychosexual impact, fertility impact, bladder function, need for further treatment, success rates (by patient), treatment complications, patient expectations, alternative surgery. **[D(GPP)] Chapter 12.3.4**

When abdominal hysterectomy is decided upon then both total and sub-total methods should both be discussed with the woman. **D[(GPP)] Chapter 12.3.4**

Pre-treatment before hysterectomy and myomectomy with GnRH-a for 3 to 4 months should be considered where uterine fibroids resulting in an enlarged or distorted uterus are present.^{xii} **[A] Chapter 12.3.4**

Women should be informed about the increase in complications with hysterectomy when uterine fibroids are present. **[C] Chapter 12.3.4**

^{xii} Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of GnRH-a is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

When surgery for fibroid related HMB is felt necessary then myomectomy, UAE and hysterectomy must all be considered, discussed and documented. **[D(GPP)]**

Chapter 12.3.4

Chapter 13 Removal of ovaries at time of hysterectomy

A full discussion before ovaries are to be removed of the impact on HRT use and other effects should take place. **[D(GPP)] Chapter 13.6**

Women should be informed of the risk of premature loss of ovarian function even when they are retained. **[D(GPP)] Chapter 13.6**

Women should be informed about the impact of bilateral oophorectomy on risk of ovarian cancer, breast cancer and uterine pathology. **[D(GPP)] Chapter 13.6**

Oophorectomy should not be undertaken with hysterectomy for HMB, without full counselling and consent. **[D(GPP)] Chapter 13.6**

Women found to have a family history of ovarian cancer should be referred for genetic counselling. **[D(GPP)] Chapter 13.6**

In women aged under 45 years considering hysterectomy for HMB and have other symptoms that may be related to ovarian dysfunction then a trial of medical ovarian suppression for 3 months should be used as a guide to the need for oophorectomy.

[D(GPP)] Chapter 13.6

Chapter 14 Competencies

Training

On appointment to a consultant post, clinicians should demonstrate completion of an accredited training programme in an established procedure and this will be assessed on acquisition of competence, prior to undertaking that procedure. **[D (GPP)]**

Chapter 14.5

Operative competence of clinician trainees undertaking procedures to diagnose and treat HMB should be formally assessed by trainers through a structured process such as that defined within training schemes of the Post-graduate Medical Education & Training Board and/or Royal Colleges. **[D (GPP)] Chapter 14.5**

Training programmes must be available of sufficient length to allow clinicians time to achieve competency in complex procedures (e.g. operations for large fibroids or when sited in an awkward position) when these are appropriate. These will usually be sited in units with a particular interest and sufficient workload to facilitate this. **[D (GPP)] Chapter 14.5**

Maintain

Maintenance of surgical or radiological skills requires a robust clinical governance framework, this will include audit of numbers, case-mix, outcomes of all treatments both at the individual operator and organisational level. These data should be used to demonstrate good clinical practice. **[D (GPP)] Chapter 14.5**

Established clinicians should be able to demonstrate that their training, experience and current practice at least equates to the standards laid out for newly trained clinicians. **[D (GPP)] Chapter 14.5**

Governance

If a clinician lacks competence to undertake a procedure then they should refer to a clinician with the appropriate skill. Organisations should be responsible through service specification based on robust audit data that identify clinicians with the appropriate skills. **[D(GPP)] Chapter 14.5**

2.3 Research recommendations

Risk factors for HMB & uterine pathology

What is the epidemiology of women presenting with HMB in primary care?

Quality-of-Life impact of HMB

- The presently available HMB/menorrhagia specific QoL measures need to be validated.
- HMB specific quality-of-life measures need to be developed for use in research and clinical practice.
- There is a need for more research on the interaction of ethnicity and the perception of HMB.

Measurement of Menstrual Blood Loss

Investigate routine use of indirect measurements of MBL in primary and secondary care.

Need for Quality-of-life research in HMB and menstruation.

Investigations for structural and histological abnormalities

The production of predictive values for HMB and significant uterine pathology in primary care populations.

Endometrial thinning as pre-treatment before endometrial ablation

Where evidence is not available on endometrial thinning prior to different ablative techniques, then it is recommended this research be undertaken.

1 **Interventions for uterine fibroids**

- 2 What effect do UAE and myomectomy have on long-term fertility of women?
- 3 What are the psychosexual impacts on UAE and myomectomy?
- 4 What are the long-term recurrence rates of fibroids after UAE or myomectomy?
- 5 How does UAE effect blood flow in the uterus?
- 6 What is the mechanism of action via which UAE reduces MBL?
- 7 What is the ovarian function after UAE or myomectomy?
- 8 What is the ovarian and uterine function of women with or without HMB?

9

10 **Hysterectomy**

- 11 An investigation into the medium and long-term outcomes of subtotal and total
- 12 hysterectomy.

- 13 An investigation into the effect of hysterectomy and oophorectomy on cancer?

14

15 **Competencies**

- 16 Volume-outcome relationships in gynaecological procedures taking into account
- 17 patient case-mix, hospital and operator factors.

18

19

1 **2.4 Algorithm**

2 **[See Separate File]**

3 Defining HMB

3.1 What is menstruation?

Menstruation is a woman's monthly bleeding from the reproductive tract, as a consequence of cyclical changes in hormonal activity. It is also called menses, menstrual period or period. When a woman has her period, she is menstruating. The menstrual blood is partly blood and partly tissue / fluid from the inside of the uterus. It flows from the uterus through the small opening in the cervix, and passes out of the body through the vagina.

3.2 “Normal” menstrual pattern

“Normal” menstrual pattern and blood loss

Beliefs derived from personal experience and cultural, social and educational influences give rise to a sense of “normal” for an individual woman. Clinicians define length of a menstrual cycle as the time from the start of a period to the start of the next.

It is not always easy to determine when a menstrual period begins or ends. This may be due to the types of bleeding a woman may experience (e.g. spotting, brown/pink discharge) and whether or not a period is regarded as a continuous bleed of a certain duration.¹⁶ It may at times be difficult to differentiate between a menstrual period and an intermenstrual bleed, which have different clinical significances. Similar difficulties exist in defining normal menstrual blood loss.

“Normal” quantity of MBL can be defined based on the distribution of objectively measured MBL for the whole population. However, the distribution of the blood loss is non-parametric and does not correlate well with the physical and psychological symptoms that a woman may experience as a consequence of blood loss outside of a statistically derived “normal” range. Therefore, studies have been undertaken that examine changes in blood chemistry that are known to have a relationship with blood loss and sense of well being.

3.2.1 Review of ‘normal’ menstrual patterns

Overview of available evidence

Four observational studies were identified that presented data on the duration of menstruation. Six observational studies were included that reported data on the length of ‘normal’ menstrual cycles. Three observational studies were included on the amount of Menstrual Blood Loss (MBL).

Normal duration of menstruation

A study of menstrual diaries (n = 179) examined the duration of menstrual bleeding. The study found the range of period duration was from 1 to 19 days (median average of 5 days), with 97% lasting between 3 to 8 days. ¹⁷ [EL = 3]

A study (n = 1472) examined menstrual histories of adolescents girls aged between 11 and 15 years old. The study found the duration of menstruation in 89% of girls was between 3 to 7 days. ¹⁸ [EL = 3]

A study (n = 2700) assessed menstrual histories of women of all ages. The study showed the mean average duration of menstruation changed from 3.9 days at aged 20, to 2.8 days at aged 40 years. ¹⁹ [EL = 3]

A study assessed menstrual histories (n = 31593 menstrual cycles) of women of all ages. The study showed the average duration of menstruation was 4.7 days in women aged between 13 to 17 years old and 4.1 days in women aged over 40 years. ²⁰ [EL = 3]

Normal cycle length

Five studies reported length of menstrual cycles, with three reporting a mean average of 28 days and one reporting a mean average of 30 days. Three smaller studies also reported figures. ¹⁹⁻²⁶ However, as many authors note, these figures are crude and the use of mean average is questionable given the skewed distribution of figures.

Several studies identified that whether cycle length was associated with age.

A study (n = 2865) examined menstrual histories to assess menstrual cycle length. The study showed between the ages of 15 to 19 the mean cycle length was 28.8 days (SD 2.9), compared to 27.5 days (SD 2.4) in women aged between 35 and 44 years old. ²⁷ [EL = 3]

A study (n = 2316) used menstrual histories to examine if menstrual cycle length was related to age. The study showed between the ages of 15 to 19 the mean cycle

length was 30.8 days (SD 3.38), with 68.4% in the 25 to 31 days range. By between 35 to 39 years of age the average cycle length was 28.5 days (SD 2.58), with 86.4% in the 25 to 31 days.²⁸ [EL = 3]

A study examined menstrual histories to assess factors associated with menstruation. The study reported a change in cycle length as age increased, from a mean average of 34.67 days (10 to 90 percentile = 28 to 44) between the ages of 13 to 17, to a mean average of 28.37 days (10 to 90 percentile = 25 to 32) between the ages of 40 to 52.²⁰ [EL = 3]

Five studies provided data on regularity of menstrual cycles.^{19;20;23;27;29} In one survey study (n = 2865) that examined menstrual cycle characteristics, the level of irregular periods reduced with age, from 20.8% between the ages 15 to 19, to 10.8% between the ages 40 to 44.²⁷ [EL = 3] Two studies recorded the variation within women between cycles.^{20;29} The data showed a tendency for a long or short cycle to be followed by a normal length cycle.

Normal menstrual blood loss

“Normal” levels of MBL can be defined based on normal distribution of MBL for the whole population. However, this does not relate to the physiological impact of MBL. Therefore, studies have been undertaken that examine changes in blood chemistry with increased MBL. Three observational studies provided assessment of MBL.

One study (n = 476) used blood tests to assess the impact of MBL on blood analyses. The study showed that haemoglobin and ferritin levels adversely change

at MBL levels of 76.4 ml. As a result, the study outlined the upper limit of the average as being between 60 to 80 ml MBL (these figures were based on a defined sub-group that excluded women with existing menstrual problems).³⁰ [EL = 3]

A study (n = 313) on women used blood tests to examine the impact of MBL on overall blood chemistry. It showed that anaemia and iron depletion occurred at two points, first around 60ml MBL and then around 120ml MBL. The study concluded that a definition around 120ml may be more useful for the treatment of HMB as this was when anaemia was most likely to occur.³¹ [EL = 3]

A study (n = 348) used blood tests to assess if changes in overall blood chemistry were associated with MBL. The study defined heavy bleeding as equal to, or greater than, 45ml but this was based on dividing the study population into equal percentile groups, rather than biological factors. This study also shows that MBL varies between cycles within the same women, with 40% of women having a 10ml difference between cycles.³² [EL = 3]

3.2.2 Evidence statement on 'normal' menstrual patterns

Evidence from large epidemiological studies shows that cycle length decreases with age, duration of period decreases with age, that MBL increases with age and regularity of cycle improves with age (up until the pre-menopausal period). Studies show that a rapid adverse change in blood chemistry occurs at two levels of MBL, these being 60ml and 120ml.

3.2.3 GDG interpretation of evidence on ‘normal’ menstrual patterns

The GDG agreed that the finding of the research provided a valid picture of the epidemiology in the general population and physiological background to HMB. The GDG highlighted that the recognition of the variability of menstrual cycles and blood loss that occurs within populations of normal women, and experienced by an individual normal woman, is important when determining clinical care.

3.2.4 Recommendations on ‘normal’ menstrual patterns

See section 3.8.2 for recommendations

3.2.5 Research Recommendations

What is the epidemiology of women presenting with HMB in primary care?

3.3 Risk factors for increased menstrual bleeding

Whilst HMB may occur in the presence of histological abnormality, the association does not necessarily imply causality. There are a number of factors that are known to be associated with HMB, and that increase the risk of an individual woman experiencing HMB.

3.3.1 Review of risk factors associated with HMB

Overview of available evidence

In total, 28 studies were included that assess risk factors associated with HMB.

Uterine Fibroids

Uterine fibroids are a commonly occurring pathology³³, and are age related.³⁴⁻³⁶

Studies also show that uterine fibroids are more common in African-Caribbean women than in white women ($p = 0.001$).³⁷

One case review study ($n = 910$) from the USA comparing women with and without uterine fibroids found that uterine fibroids were associated with increased MBL (RR of menorrhagia where no fibroids present = 1, and where largest fibroid > 5cm = 2.4).

³⁸ [EL = 2+]

One epidemiological study (n = 50) undertaken in the UK on women with uterine fibroids, assessed the association with MBL. The study showed that site, size and number of fibroids are linked to the level of MBL.³⁹ [EL = 3]

Three observational studies showed that uterine fibroids are associated with menorrhagia (with rates between 27% to 54% found).⁴⁰⁻⁴² However, one diagnostic study highlighted that fibroids were not a common cause of adolescent menorrhagia.

⁴³

Age

Eleven observational studies examined the relationship between MBL and age.
^{20;30;32;44-51}

One study from Sweden examined the use of the alkaline haematin test on women, to measure menstrual patterns. The study (n = 476) showed a rise from 33.8ml at age 15 to a peak of 49.7ml at aged 30, before falling back to 42.7ml at aged 45.³⁰ [EL = 3] Studies using subjective measures also showed an increase in MBL with age.³² One study showed MBL increased with age (p = 0.002) (46.8% of 18 to 24 years olds and 53% of 45 to 54 years old reported HMB).⁴⁶ However, three studies showed no association between age and MBL.⁴⁹⁻⁵¹

Polyps

No studies were identified that linked presence of uterine polyps with HMB.

Blood disorders

One systematic review and two observational studies showed that inherited blood disorders, such as Von Willebrand's Disease (vWD), are associated with higher MBL, with a prevalence of 13% to 15.4% of vWD in women with menorrhagia⁵²⁻⁵⁴ [EL = 2+, EI = 2-; EL = 3] compared to the general population.⁵⁵ [EL = 3]

One comparative cohort study (n = 244) compared the prevalence of vWD in women with and without menorrhagia. The study calculated that the OR for having vWD in women with menorrhagia compared to women without menorrhagia was 8.6 (95% CI 1.3 to 194.6). {24169} [EL = 2+]

Thyroid Disorders

One study (n = 428) found no association between thyroid disorders and presence of bleeding disorders. {24845} [EL = 2+]

Endometriosis/adenomyosis

The main presenting symptom for endometriosis is usually dysmenorrhoea, but two studies show that HMB may be a significant secondary symptom. One observational study (n = 315) showed that endometriosis was associated with higher PBAC scores (110 vs. 84, p = 0.007), when compared with a non-endometriosis group. {23858} [EL = 2-] One study (n = 215) shows that 73% of women with endometriosis have a history of menorrhagia.⁵⁶ [EL = 3] One retrospective study (n = 1542) on results of pathology tests found that of 134 women with DUB 33 had endometriosis.⁵⁷ [EL = 3]

Racial group

Four observational studies from the USA and Egypt show some association between racial group and MBL,^{49;50;58;59} with one study finding an OR 4.99 (2.07-12.05) for hyper-menorrhea in non-Caucasians compared to Caucasians. However, this study did not allow for prevalence of underlying conditions.⁵⁸

Ethnic or cultural group

No evidence was identified on how perceptions of MBL changed in relation to ethnicity or socio-cultural factors.

Parity

Two observational (n = 344; n = 774) studies show a small association between number of pregnancies and MBL.^{50;60} [EL = 3; EL = 3] However, one study (n = 182) using regression analysis, found that once age was taken into account there was no association between parity and MBL.⁴⁸ [EL = 3]

Lifestyle

Three observational studies have shown that lifestyle may impact on MBL. One study found (n = 2912) that amongst US naval personnel, self-reported MBL was increased by smoking, OR = 1.17 (p<0.001), and high alcohol consumption, OR 1.4 (P<0.05).⁴⁹ [EL = 3] A second study (n = 399) calculated that women working with dry-cleaning chemicals had an OR of 3.0 of having HMB compared to controls not doing so.⁶¹ [EL = 2-] One study shows weight may be an issue.⁶² (EL = 3; n = 2663) However, these data are limited in terms of applicability.

Genetics:

No studies were identified that linked genetic factors, other than those associated with race or blood disorders, with HMB.

Help seeking and mental health

Several observational studies have examined the relationship between mental/emotional health, HMB and consultation behaviour. In studies on women who seek help it is important to control for consultation behaviour, which is known to be independently associated with psychological distress.

The reporting of symptoms in general, in community surveys, has shown an association with levels of psychological distress. Similarly, community studies have shown that women who report HMB have higher rates of psychological distress than those who do not.⁶³⁻⁶⁵ It is not known in community populations if increased MBL causes mental/emotional problems, or if mental/emotional problems increase the reporting of HMB or both. One study suggests that in some women in the community, psychological distress occurs before the reporting of menorrhagia.⁶⁴

One cohort study (n = 1517) from the UK, on women aged between 20 and 59, examined the association of menstrual and mental health problems. The study found that when asked to assess their MBL: 19% said it was light; 51.3% moderate, 24.3% heavy and 5.4% very heavy. The study found an association between classification of depression (GHG of >12) and MBL level ($\chi^2 = 20.11$, $p = 0.0002$).⁶³

[EL = 2-]

A study reported results from three case-control populations from the UK (n = 186, n = 160, n = 494) of women with or without menorrhagia to examine the impact of MBL on QoL. The study found evidence that the impact of HMB on QoL was related to women seeking medical attention.⁶⁴ [EL = 2-]

A case-control (n = 645) compared the QoL of women consulting for HMB against women consulting for other reasons. In a regression analysis, the study found that there was no association between GHQ scores and consulting for HMB or not (GHQ = <4 or >4: consulting vs. consulting controls OR = 1.26 (95% CI 0.74-2.13) and consulting vs. non-consulting controls OR = 1.43 (95% CI 0.85-2.38).⁶⁵ [2+]

In women consulting primary care for HMB, studies found that psychological distress was not a predictor for future consultation⁶⁶ but that it has a small influence on the health care sought around the time of consultation, over and above that associated with consultation behaviour.⁶⁵ The main motivation for consultation was interference in life from heavy periods. The group also found no difference in the presence of a past psychiatric disorder compared to women consulting with an illness other than HMB.⁶⁴ The higher levels of psychological distress were felt to be related to the profound way in which menstrual disturbances affect a woman's life.

In secondary care, two studies (n = 521; n = 226) found only limited association between mental health and MBL.^{67;68} [EL = 2- EL = 2-] However, two studies (n = 50; n = 44) showed that higher MBL is associated with worse mental health scores, although there was no control for consultation behaviour.^{69;70} [EL = 2-; EL = 2+]

3.3.2 Evidence statement on risk factors for HMB

Evidence shows that the presence of uterine fibroids, increased age and racial group are linked to the likelihood of women having HMB (although these factors may themselves be related). Evidence also shows that psychological well-being factors are likely to moderate an individual woman's response to her MBL. However, for many of these factors, their role in causality and the effect of modifying them has yet to be elucidated.

3.3.3 GDG discussion on risk factors for HMB

The GDG highlighted that socio-cultural factors also influence an individual woman's response to MBL, and that this must be taken into account during consultation.

3.4 Prevalence of uterine pathology

Studies on populations of women with “normal” menstrual patterns indicate that variability and change in menstrual blood loss are common. Studies on women who have potentially life threatening disease suggest that these symptoms may indicate the presence of serious uterine pathology. It is important to estimate the likelihood that a woman with HMB will have uterine pathology, as this will affect management decisions. Knowledge of the prevalence (“pre-test probability”) within the group of women to whom the process is applied, is part of the assessment.

3.4.1 Review of uterine pathology

Overview of available evidence

In total, 20 observational and diagnostic studies were included in this section. These present data on presence of pathology, but the results are dependent on the accuracy of the investigations used and the selected nature of the study populations (In most cases a woman is referred for investigations because a clinician suspects pathology).

Uterine pathology

A diagnostic case-review (n = 1202) from the Netherlands on women with AUB examined the use of hysteroscopy to assess levels of uterine pathology. The study found that of 502 women referred with menorrhagia, 267 (53%) had non-significant pathology, 137 (27%) had submucous myomas and 20% had other pathology.⁴² [EL = 3]

1 A diagnostic Randomised Control Trial (RCT) (n = 683) undertaken in the UK on
 2 women with Abnormal Uterine Bleeding (AUB) was identified. From the figures for
 3 levels of pathology identified, it was possible to calculate basic prevalence levels. In
 4 a moderate risk group (pre-menopausal, >40 years old) it was found that 11.5% had
 5 endometrial/uterine polyp, 36% had uterine fibroids, 1% had endometrial cancer and
 6 1% had hyperplasia. For the low-risk group (pre-menopausal, <40 years old, no
 7 other risk factors), 6% had endometrial/uterine polyp, 19% had uterine fibroids, 0%
 8 had endometrial cancer and 0% had hyperplasia. The high risk group covered post-
 9 menopausal women, and therefore is not shown here.⁷¹ [EL = Ib]

11 A diagnostic study (n = 793) undertaken in Italy involving women with menorrhagia,
 12 examined the use of hysteroscopy and ultrasonography to assess uterine pathology.
 13 The study found that 325 had normal findings and 445 had abnormal findings (234
 14 [29.5%] with submucous myomas, 155 [19.5%] with endometrial polyps, 76 [9.5%]
 15 with endometrial hyperplasia (of any type) and 2 [0.2%] with endometrial carcinoma).
 16 ⁷² [EL = II]

18 A diagnostic study (n = 2500) undertaken in the UK on women referred for
 19 hysteroscopy, found the following diagnostic findings in 1120 women referred with
 20 menorrhagia: 583 (52.1%) had normal results, 334 (29.8%) had uterine fibroids, 112
 21 (10%) had polyps, 8 (0.7%) had atrophy, 29 (2.6%) had irregular endometrium, 3
 22 (0.3%) had endometrial carcinoma and 51 (4.6%) were classified as miscellaneous.
 23 ⁷³ [EL = II]

1 A case-series of women (n = 1029) from the UK who had undergone diagnostic D&C
 2 found that 281 of 1029 (27.4%) had 'failed' (procedure not complete or no suitable
 3 material retrieved), 627 (60.9%) had normal results, 57 (5.5%) had non-specified
 4 hyperplasia, 8 (0.8%) had endometriosis, 21 (2.0%) had endometrial polyps, 15
 5 (1.4%) had endometrial carcinoma, 8 (0.8%) had atrophic endometrium and 12
 6 (1.2%) had others conditions. However, this study was not specifically on women
 7 with menstrual problems, so results have to be extrapolated. ⁷⁴ [EL = III]

9 A retrospective case-series of women (n = 139) from Switzerland with AUB
 10 examined the diagnostic use of histopathological analysis. The results showed that
 11 33 (24%) women had polyps, 22 (16%) had submucous fibroids and 5 (3.6%) had
 12 endometrial hyperplasia. ⁷⁵ [EL = II]

14 A diagnostic study (n = 419) undertaken in the USA on pre-menopausal women
 15 examining the use of hysteroscopy, D&C or biopsy for identification of uterine
 16 pathology, was identified. The study found that of 415 women examined: 165 (39%)
 17 had endometrial polyps, 68 (16%) had submucous leiomyomas and adenomatous
 18 hyperplasia 16 (8.5%). However, this study was not specifically focussed upon
 19 women with menstrual problems. ⁷⁶ [EL = II]

21 A case-series of women (n = 2581) undertaken in the UK with menstrual problems
 22 examining the use of hysteroscopy for identification of uterine pathology, was
 23 identified. The study found that 11.4% had submucous fibroids, 10.6% had polyps,
 24 and 1.6% had endocervical polyps. The study assessed differences between pre
 25 and post-menopausal women, and found that 22% of post-menopausal vs. 3.4% pre-

menopausal had hyperplasia (of any type). The study also found that submucous fibroids were more common in pre to post-menopause (11.8 vs. 10.7; $p = 0.43$) and that polyps were more common in post to pre-menopause (13.9 vs. 8.9%; $p = 0.0001$).⁷⁷ [EL = III]

A case-series of women ($n = 215$) diagnosed with endometritis found that 76% had a history of menorrhagia.⁵⁶ [EL = 2-]

A diagnostic study found, in an AUB population, a prevalence of endometriosis of between 18.3% and 15.4% in the two groups studied. (EL = Ia; $n=275$).⁷⁸

A diagnostic study ($n = 310$) undertaken in Canada on women with AUB used endometrial biopsy to assess presence of no pathology. The study found that of those tested: 266 (85.8%) had normal pathology, 8 (2.6%) had hyperplasia, 9 (2.9%) had complex hyperplasia and 4 (1.3%) had hyperplasia with atypia.⁷⁹ [EL = III]

A diagnostic study ($n=43$) undertaken in Italy on women with menorrhagia compared ultrasound and histology techniques. The study found that 46.5% had histopathology confirmed adenomyosis.⁸⁰ [EL = II]

A diagnostic study ($n=102$) undertaken in Italy on women with menorrhagia compared results from ultrasound and endometrial biopsy. The study found the prevalence of adenomyosis was 28% (29/102 women).⁸¹ [EL = Ib]

1 A cohort study (n = 180) compared prevalence of pathology in women with and
2 without AUB. The study found a higher rate of pathology in women with AUB (p <
3 0.05).⁸² [EL = 2=]

4
5 A diagnostic study (n = 370) in a group of women with AUB referred for hysteroscopy
6 found that 33.51% had a normal cavity and the rest had some form of pathology.
7 However, these findings are from a highly selected secondary care group.⁸³ [EL = II]

8
9 A retrospective case-series (n = 3241) of women with menorrhagia referred for
10 investigation for endometrial cancer found no cases reported.⁸⁴ [EL = 3]

11
12 A retrospective case-series (n = 1033) of women with heavy or irregular bleeding
13 referred for investigation found that 5 had endometrial cancer and 45 had
14 hyperplasia. The risk factors associated with cancer were weight, family history, age
15 and infertility.⁸⁵ [EL = 3]

16
17 A diagnostic study (n = 187) on women with AUB found the following pathology
18 amongst women with menorrhagia: 68 had normal pathology, 13 had polyps, 16 had
19 fibroids, 3 had hyperplasia, and 2 had endometriosis.⁸⁶ [EL = II]

20
21 A retrospective case-series (n = 665) identified that uterine pathology was more
22 likely in women over 40 years of age compared to those under 40 years of age (32%
23 vs. 21%).⁸⁷ [EL = 3]

A retrospective case-series (n = 660) on women with DUB found 124 had endometrial hyperplasia, 103 had myomas, 24 had adenomyosis, 20 had endometriosis, 32 had polyps, 6 had cysts of ovary, and 9 had carcinoma.⁸⁸ [EI = 3]

Endometrial carcinoma

Given the morbidity and mortality associated with endometrial cancer it is important to assess this pathology in further detail. The incidence of endometrial cancer in England & Wales is shown in table 2.1. What this shows is an age-related increase in incidence.

Table 2.1 - endometrial cancer incidence by age per 100000

Age range	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69
Rate of corpus uteri cancer	0.2	0.6	1.2	2	4.1	11	28.4	50.2	59.8	67.8

(Source: Series MB1 no. 34 ONS Cancer statistics Registrations 2003.)⁸⁹

Lifetime risks of endometrial cancer reinforces the incidence findings. The lifetime risk of endometrial cancer for women at different ages in the USA, and Scotland (figures not available for women under 64) are shown in tables 2.2 & 2.3. The figures for Scotland show a lower rate of cancer in than in the USA.

Table 2.2 – Lifetime risk of endometrial cancer in USA (%)

Age	30	35	40	45	50	55	60	65	70	Whole life
Lifetime risk of corpus uteri cancer (%)	0.01	0.03	0.06	0.13	0.25	0.45	0.76	1.14	1.52	2.61

(Source: NOS Cancer by Race, Females SEER 13 Registries for 2000-2002) ⁹⁰

Table 2.3 – Lifetime risk of endometrial cancer in Scotland

Age	64	74	84	Whole life
Lifetime risk of corpus uteri cancer (%)	0.7	1.1	1.3	1.4

(Source: Scottish Cancer Registry, ISD. Data extracted: October 2004) ⁹¹

However, this does not show the incidence and risk amongst women with HMB. The RCOG guidelines on HMB estimated that in women aged between 35 and 54, 8 of every 10000 women who presented with HMB would have endometrial carcinoma. ⁹² This was based on the incidence of endometrial carcinoma of 38% in women with HMB, 1987 incidence of cancer, and the frequency of consultation in primary care with HMB of 5%. These figures have been up-dated with 2003 data (the latest available). In women aged less than 30 the estimate shows a percentage less than 0.01 or 1 per 10000. The rates of endometrial carcinoma likely to be present per 10000 consultations for HMB for older age-groups are:

1 **Table 2.4**

Age range	30- 34	35- 39	40- 44	45- 49	50- 54	55- 59	60- 64
Rate of endometrial cancer per 10000 consultations	1	1	3	8	20	36	42

2

3 These figures probably over estimate the incidence in the HMB population, as the
4 prevalence figures are based on women with endometrial carcinoma reporting HMB
5 rather than women with HMB having endometrial cancer, which would be a more
6 relevant measure. One study from a secondary care setting found that 5 of 987
7 (0.5%) of women with confirmed menorrhagia had endometrial cancer, and a further
8 45 (4.5%) had hyperplasia.⁸⁵ If these figures are used instead of the 38% previously
9 used then the rates per 10000 would be all be less than 1. Indeed, there is no clear
10 data linking HMB to endometrial cancer, with most studies concentrating on irregular
11 bleeding^{93,93-95} or not assessing menstrual symptoms.⁹⁶

12

13 In addition, NICE have produced guidelines for the referral of women with suspected
14 malignancy from primary care, and have concluded that this is necessary in women
15 with persistent intermenstrual bleeding. This infers that in women with a normal
16 pelvic examination, other symptoms of vaginal bleeding do not require investigation
17 or referral from primary care.⁹⁷

18

19 **3.4.2 Evidence statement of uterine pathology**

20 The results of 20 observational and diagnostic studies show that the majority of
21 women with HMB have no histological abnormality that can be implicated in causing
22 HMB. Uterine fibroids (approximately 30% of women) and polyps (approximately

1 10% of women) are the most common form of pathology found. It is rare for a
2 woman who has presented with HMB and has undergone investigations, to have an
3 underlying pre-malignant or malignant condition. However, there is lack of research
4 on the prevalence of significant uterine pathology in primary care populations which
5 hinders the production of predictive values for use in primary care.

7 **3.4.3 GDG interpretation of evidence of uterine pathology**

8 The GDG agreed that the findings of the research provided a valid picture of the
9 presence of significant uterine pathology.

10
11 The GDG highlighted that the assessment of hyperplasia now focuses upon
12 differentiating between normal and atypical types; as atypical hyperplasia has been
13 shown to be closely linked to the development of future malignancy.

3.5 Quality-of-Life impact of HMB

A basic reason for people seeking help for a health condition is the perceived impact it is having on their quality-of-life, and this concept has been recognised and used in health psychology models, such as the Health Belief Model. It is therefore important to assess the impact that HMB has on QoL.

3.5.1 Review of quality-of-life associated with HMB

Quality of life measures for women with HMB

One systematic review shows limited use of QoL measures, mainly SF-36, with no accepted menorrhagia or MBL specific measures.⁹⁸ [EL = 2++]

Four studies have examined the use of QoL measures in menorrhagia.⁹⁹⁻¹⁰² One study examined the use of SF-36 for menorrhagia. Of 8 scales in SF-36, two (mental health and general health perceptions) had lower internal reliability with menorrhagia women compared to the general population: 0.5 vs. 0.83 and 0.51 vs. 0.8. The study concluded that SF-36 is not relevant enough to reflect the QoL issues of women with menorrhagia.⁹⁹

Overview of available evidence

No systematic reviews were identified on QoL impact, but 15 observational studies were identified that examined or measured quality of life associated with HMB. In addition, a number of interventional studies have used QoL as a primary outcome measure, and the baseline data may be used to show the impact of HMB.¹⁰³⁻¹⁰⁹

Quality-of-life of women with HMB

Three qualitative studies (n = 200; n = 30; n = 43) using interviews and focus groups, showed the experience of women with menorrhagia. These studies showed that impact involves physical, psychological and social factors – with women talking about amount of blood loss, mood changes and becoming self-conscious. In terms of accessing services, women made it clear that more information was required with more acceptance and understanding of the problem by clinicians.¹¹⁰⁻¹¹² [EL = 3; EL = 3; EL = 3]

Six studies showed an association between HMB and mental well-being.

Using a regression model, a cross-sectional study (n = 865) from the UK found that unemployment was a predictor of MBL greater than 80ml.¹¹³ [EL = 3]

In a second publication (n = 952), the study highlighted that the relationship between MBL and QoL was not a linear relationship, showing that impact on QoL was the same for women with MBL between 50 ml and 200 ml.¹¹⁴ [EL = 3]

A study from the UK (n = 840) showed the impact HMB had on women and the reasons why women consulted for HMB. These showed that physical and social issues, but not psychological, were the main causes of seeking help (performance of house work, p = 0.03; days off work, p = 0.56; life causing embarrassment, p = 0.02; mood, p = 0.53; sex life, p = 0.12; social life, p = 0.01).⁶⁴ [EL = 2-]

One cross-sectional survey (n = 2805) from the USA showed HMB was associated with lower employment rates, an average 3.6 weeks labour lost per year and lost earnings of \$1692 per year. The study found that women with menorrhagia rated their overall health lower than the general population (fair = 40 [10.7%] vs. 149 [6.1%]; poor = 16 [4.3%] vs. 32 [1.3], $p < 0.001$). The study also calculated the OR for risk factors of being in the labour force and found heavy periods had an OR of 0.72 (0.56 to 0.92).¹¹⁵ [EL = 3]

A survey (n = 200) undertaken in Egypt showed that with relation to gynaecological symptoms, menstrual disturbances and heavy menstrual bleeding were rated as the most important concerns of women.¹¹⁶ [EL = 3]

An observational (based on an RCT) study (n = 220) from Finland showed that the main impact of HMB were physical and social issues, but not psychological. However, other studies showed HMB is associated with worse psychological scores, although the causal pathway and direction were not established.⁶⁸ [EL = 2-]

One study found (n = 348 and n = 209) the following QoL problems amongst women with menorrhagia: ('flooding' = 71%; clothes bloodstained = 58.9%; painful periods = 52%; cause of anxiety or depression = 50.3%; cause of moodiness or irritability = 68.4%; Interfere with social life = 29%; Interfere with hobbies = 34.2%; interfere with life in general = 43.4%).^{117;118} [EL = 3 and EL = 2-]

Results from several interventional studies (n = 50, n = 197, n = 63) that used quality-of-life measures as the primary outcome, also highlight the level of impact that HMB has on a woman's life. ¹¹⁹⁻¹²¹ [EL = 3, EL = 1+, EL = 1+]

3.5.2 Evidence statement on quality-of-life associated with HMB

Evidence shows that HMB has a measurable effect on quality-of-life. There is evidence that HMB impacts on social interaction, and though not perceived by women to affect work performance, evidence shows an association with higher unemployment and absence from work. It appears that it is social and physical impacts of HMB that cause women to seek help.

3.5.3 Recommendations on quality-of-life associated with HMB

See section 3.8.2 for recommendations

3.5.4 Research recommendation on quality-of-life associated with HMB

- The presently available HMB/menorrhagia specific QoL measures need to be validated.
- HMB specific quality-of-life measures need to be developed for use in research and clinical practice.
- There is a need for more research on the interaction of ethnicity and the perception of HMB.

3.6 Measurement of Menstrual Blood Loss

There are several frameworks for analysing the consultation between the doctor and the woman. One commonly used approach is to recognise consultation styles as using a biological model where physical processes are measured and compared to a “normal” reference, and a psychosocial model where the woman’s psychological disturbance and social impairment are the focus. In reality, most clinicians use a combination of the two models.

This difference in consultation styles has manifested itself in the controversy that exists between advocates of measuring the amount of menstrual blood loss and those that feel this is irrelevant in managing the psychosocial problems that a woman presents. Measurement of menstrual blood loss can be divided into three types. First, the objective measurement of MBL via the collection of used sanitary material from the woman from which blood content is estimated. Second, is the surrogate measurement of MBL using duration of menstruation or number of sanitary products used. Third is the subjective assessment of MBL via women’s estimated amount of menstrual material.

3.6.1 Review of measurement of Menstrual Blood Loss

Direct measurement of MBL – alkaline haematin

Evidence from six diagnostic studies shows that the estimation of MBL from sanitary material using the alkaline haematin test, is an accurate and precise method to use.¹²²⁻¹²⁷ [EL = III, EL = III, EL = II, EL = III, EL = II, EL = III] Three of these studies on the alkaline haematin method showed recovery rates between 95% and 105% of known blood totals.¹²²⁻¹²⁴ [EL = III, EL = III, EL = II] One concern with direct MBL

measurement is that extraneous blood (blood passed but not collected on pads) is not collected on pads/towels. One study estimates that this can have a significant impact on the total. ¹²⁸ [EL = II] Two small observational studies in secondary care showed that formally measuring MBL and informing women of whether they had normal or heavy menstruations, did have an impact upon future treatment decisions. ^{129;130} [EL = 2-, EL = II]

However, two qualitative studies (n = 73; n = 20) highlighted the impracticality of using direct material measures outside a research study. ^{131;132} One study found that GPs also stated that the most important factor in decision-making was whether MBL interfered with daily life rather than the amount of MBL. ¹³¹ [EL = 3] Another study showed that community medical practitioners found that medical definitions were unhelpful, there was a lack of standards of normality and difficulties in discussing menstruation, which resulted in individual practitioners making judgements in idiosyncratic ways. ¹³² [EL = 3]

Indirect measurement of MBL - Pictorial Blood Loss Assessment Chart (PBAC)

Given that sanitary product recovery methods may have limited use in clinical practice, other methods have been developed. These methods focus on indirect measures or self-assessment. The most studied of these methods is the Pictorial Blood Loss Assessment Chart (PBAC), first outlined in 1990. ¹³³

Six diagnostic and observational studies were identified examining the use of PBAC. Due to the heterogeneity of the study populations it was not possible to undertake a meta-analysis of these studies. ^{126;128;133-136}

The original study (n = 18 women, 55 cycles) undertaken in the UK investigated the use of PBAC compared to alkaline haematin, used a cut-off of greater or equal to 100 compared to an alkaline haematin cut-off of 80ml and obtained a correlation score of $r = 0.847$. The study found that the sensitivity of PBAC was 86% and specificity was 89% (based on >100 PBAC score = >80ml).¹³³ [EL = II]

A second study (n = 288 women) investigating the use of PBAC compared to alkaline haematin showed that the sensitivity and specificity of PBAC were maximised at a score of 130. Furthermore, the study found that positive and negative predictive values were maximised at a PBAC score of 185.¹²⁶ [EL = II]

A third diagnostic study (n = 103) investigating the use of PBAC compared to alkaline haematin, showed that using a cut-off of 100 on PBAC gave a sensitivity of 97%, and specificity of 7.5%, a positive predictive value of 62%, and a negative predictive value of 60% and a correlation coefficient of 0.4659.¹³⁴ [EL = II]

A fourth study (n = 56) investigating the use of PBAC compared to alkaline haematin, using a regression analysis, found an association between PBAC scores to MBL ($p = 0.001$). At a PBAC score greater than or equal to 100, sensitivity = 88%, specificity = 52%, false positive = 59%.¹³⁵ (EL = III)

A fifth study (n = 307) compared PBAC to alkaline haematin, and found a sensitivity of 58% and specificity of 75% at a PBAC score cut-off of 50.¹³⁶ [EL = III]

A sixth study (n = 121) compared PBAC to alkaline haematin, and found sensitivity of 86% and specificity of 88% where PBAC was greater than or equal to 100 and MBL was equal or greater than 80ml. The study also assessed the inclusion of extraneous blood loss during change of pads or other loss. With no extraneous blood loss, it was estimated that 22 of 61 women presenting with menorrhagia had MBL greater than 80ml. When extraneous blood loss estimation was include then 45 of 61 had MBL greater than 80ml. ¹²⁸ [EL = II]

Table 3.1 provides a summary of the available evidence on PBAC. These results show a lack of consistency across the studies.

Table 3.1 – Summary of evidence on PBAC

Reference	Number of participants	PBAC level for menorrhagia	Comparator measure	Sensitivity (%)	Specificity (%)
¹³³	18	100	Alkaline haematin	86%	89%
¹²⁶	288	100	Alkaline haematin	91%	81.9%
¹³⁴	288	130	Alkaline haematin	97%	7.5%
¹³⁵	53	185	Alkaline haematin	88%	52%
¹³⁶	103	50	Alkaline haematin	58%	75%
¹²⁸	53	100	Alkaline haematin	86%	88%

Surrogate and self-assessment measures

Eight observational studies were identified examining the use of surrogate or self-assessment of MBL. ^{47;51;113;126;137-140}

One study (n = 92) showed that there is limited correlation between self-assessment, quantity of sanitary towels used, duration of menses and objective MBL (where 23 of 68 (34%) cycles termed light were greater than 80ml; 28 of 59 periods (47%) termed heavy were less than or equal to 80ml; 32 of 57 termed medium were greater than 80ml).¹³⁸ [EL = II]

An observational study (n = 69) showed that women were able to differentiate 'lightest' from 'heaviest' periods during a study (p < 0.001), with 45% correctly assessing the order of MBL for all four periods.¹³⁹ [EL = III]

An epidemiological study was conducted (n = 5292) in order to investigate whether there was a relationship between MBL and duration of menses. The study did find a correlation between the duration of menses and MBL (n = 420): r = 0.35, p < 0.01.¹³⁷ [EL = 3]

A study (n = 412) found associations between pad use and MBL: r = 0.61, p < 0.005, and between duration and MBL (n = 420): r = 0.35, p < 0.01.⁴⁷ [EL = III]

An observational study (n = 254) found a relationship between duration of menses and MBL (periods lasting 3 days = 24.3ml and periods lasting 6 days = 58.66ml).⁵¹ [EL = III]

A study (n = 952) found in a regression model that clot size, ferritin level and frequency of pad change (p = 0.001, 0.002, 0.006, respectively) provide the best predictive model for MBL > 80 ml.¹¹³ [EL = 3]

A study (n = 288) found that 66 (56%) women complaining of menorrhagia had ml >80ml, 52 (44%) women complaining of menorrhagia had MBL <80ml. In comparison, 23 (13.5%) women who did not complain of menorrhagia had MBL >80ml, and 147 (86.5%) who did not complain of menorrhagia had MBL <80 ml. ¹²⁶ [EL = II]

A study (n = 32) compared women's own estimation of MBL against objective measurement of MBL. The study found a correlation between women's recall and actual menstrual blood loss (p < 0.001). ¹⁴⁰ [EL = III]

3.6.2 Evidence statement on measurement of Menstrual Blood Loss

Diagnostic studies show that direct material measurements are accurate and precise measures of MBL, the only concern being that all material is collected. The PBAC has been shown to be highly variable, with no study finding the same delineation point. Use of surrogate or indirect measures shows some correlation, but there is high variation between studies and only weak correlations.

3.6.3 GDG interpretation of the evidence on measurement of Menstrual Blood Loss

The GDG placed a high value on the practical use of any measure in clinical practice. If a measure cannot be used in routine practice then it is of limited value. The GDG felt that use of direct menstrual material measures was impractical in clinical practice, and would have little impact on management strategies.

3.6.4 Recommendations on measurement of Menstrual Blood Loss

See section 3.8.2 for recommendations

3.6.5 Research recommendation on measurement of Menstrual Blood Loss

- Investigate routine use of indirect measurements of MBL in primary and secondary care.
- Need for Quality-of-life research in HMB and menstruation.

3.7 Prevalence of HMB

The section above highlights the impact that HMB has on the individual woman but does not address the population impact of HMB. Therefore, it is important to ascertain the population impact of HMB.

3.7.1 Review on prevalence of HMB

Overview of available evidence

One systematic review and seven observational studies were found that reported data on the prevalence on HMB.

Prevalence of HMB

The review reported prevalence of excessive menstrual bleeding of 4% to 9% from four studies. The review also reported on two WHO studies that outlined HMB rates of 8% to 27% based on subjective assessment.¹⁴¹ The WHO studies were undertaken in various locations around the world, and therefore the results may reflect the socio-cultural differences in how menstruation is perceived.

The primary studies reported rates of HMB of 11% to 51.6%, however, it is likely that differences in how menstruation is measured and the populations sampled will account for some of the variation.^{19;20;30-32;45;48;85;142;143}

Three studies objectively measured MBL.³⁰⁻³² The others used self-assessment methods.^{19;20;45;142} Of the three measures that used objective measures, the first study (n = 476) found 11% had an MBL greater than 80ml.³⁰ [EL = 3] The second

publication (n = 182) reported that 13.5% of women had an MBL greater than 80ml.
³¹ [EL = 3] The third study (n = 348) found 26 of 280 (9%) had an MBL greater than
 80 ml. ³² [EL = 3]

Of the subjective studies, one study (n = 1513) reported prevalence of HMB of
 51.6% and of 'increased' menstrual bleeding within the last 6 months of 22.6%. At
 the 12-month follow-up, the study showed an incidence of HMB of 25% and for
 'increased' menstrual bleeding of 20.5%. ⁴⁶ [EL = 3] A second study (n = 1517)
 found self-reported rates of heavy menstrual bleeding of 24.3%, and of very heavy
 menstrual bleeding of 5.4%. ⁶³ [EL = 3] A third cohort study (n = 5292) found 19.5%
 of women reported heavy periods. ¹³⁷ [EL = 3] A fourth study (n = 3096) found 21%
 of women reported heavy periods. ¹⁴⁴ [EL = 3] A fifth study (n = 4610) found that
 30% of women reported having heavy periods. ¹⁴³ [EL = 3]

3.8 Definition of HMB

The sections above outline both the objective and subjective elements needed for defining HMB. There is some evidence that women and clinicians find some of the definitions currently used for HMB unhelpful.^{131;132} Terms and definitions of symptom complexes are required to allow better communication between women and clinicians and the prediction of the presence of serious pathology. One study demonstrates that quality-of-life and MBL are not closely linked.^{113;114} Another study shows that the direct measurement of MBL in clinical settings is impractical.¹³¹

3.8.1 Evidence statement on definition of HMB

The sections above provide the information for a clinically useful definition of HMB to be made. This is different from the definition used in research studies, which is currently set at between 60ml and 80ml per menstruation. The reasons for not adopting this research definition are that HMB is a highly subjective and personal issue and the current objective measurements of HMB are not practical in the clinical setting. The primary aim of any treatment and care is that it is responsive to the physical, social and emotional experiences a woman has, rather than being determined by objective measurements defined by a test. It is therefore important that any definition of HMB recognises the subjective experiences of women in treating HMB.

3.8.2 Recommendations on definition of HMB

For clinical purposes, HMB is defined as excessive menstrual blood loss leading to interference with the physical, emotional, social and material quality-of-life of a woman, and which can occur alone or in combination with other symptoms. **[D]**

HMB should be recognised as having a major impact on a woman's quality of life.

[C]

When deciding care options, clinicians should take into account the range and natural variability in menstrual cycles and blood loss in an individual woman and within normal populations. **[D(GPP)]**

A successful treatment outcome is determined by the woman with HMB. **[D(GPP)]**

Uses of direct or non-direct measurement techniques for MBL are not routinely recommended in women presenting with HMB. **[D(GPP)]**

4 Investigations for HMB

Pathology in HMB may result as a consequence of the blood loss, cause the excessive blood loss or be associated with the condition and have no direct role in causality. The role of investigations is to detect pathology that may be causing symptoms and to detect pathology that may progress to cause significant illness. Interventions that correct the pathological abnormality are designed to remove the underlying condition and improve or prevent deterioration in health.

In the majority of women who experience HMB, pathology that results from, or causes excessive blood loss cannot be identified (see Chapter 3). For those women in whom pathology is identified, treatment targeted at the abnormality may give rise to significant health gains. In contrast, some women may have the same pathology and not suffer from HMB or persist with HMB even when the pathology is corrected.

Investigations should be directed towards pathology that is correctable and the treatment of which results in health gains or the prevention of illness.

4.2 History taking for HMB

The aim of history taking is to define the presenting condition as one of HMB, determine the problems that it is causing the woman and detect symptoms that may indicate significant pathology.

4.2.1 Review on history taking for HMB

Overview of available evidence

No evidence was identified relating to the history taking for women who present with HMB. Therefore, this section was based on discussion within the GDG.

4.2.2 GDG discussion on history taking for HMB

The GDG identified three main areas of questioning.

1. Nature of bleeding

Initially the clinician should establish that the woman has menstrual bleeding, that is, in her and the clinicians' opinion, heavy (see section 3.9.2).

Whilst non-menstrual bleeding is outside the scope of this guideline, epidemiological evidence suggests an alteration in the menstrual cycle, intermenstrual bleeding and post coital bleeding may be the first symptoms of gynaecological cancer and indicate the need for a pelvic examination.⁹⁷ Persistent intermenstrual bleeding requires investigation to exclude malignancy.⁹⁷

2. Symptoms suggesting possible significant pathology

The GDG felt that pelvic pain and pressure effects should be investigated, as these may indicate presence of uterine pathology or disorders.

3. Other features that may determine treatment or other action

It is important for the clinician to explore the woman's perspective. By exploring the woman's ideas, concerns and expectations regarding HMB and its treatment, the requirements of therapy, education and reassurance may be determined. In addition, a clinician should illicit what treatment the woman has already used, if any.

In addition, the GDG felt that issues, such as age, up-to-date smear test and family history of pathology, and future fertility and contraception plans should be ascertained.

4.2.3 Evidence statement on history taking for HMB

Based on GDG discussion, history taking for HMB should cover three main objectives: to define the nature of bleeding; identify potential pathology; and identify women's ideas, concerns, expectations and needs.

4.2.4 Recommendations on history taking for HMB

History taking should cover: the nature of bleeding problem; symptoms suggesting potentially serious pathology; and other factors that will determine treatment options.

[D[GPP]]

If history taking reveals HMB without the presence of pathology, then there is no need to undertake a physical examination prior to initiating first-line medical treatment. **[D (GPP)]**

1
2 If history taking suggests pathology with symptoms such as inter-menstrual or post
3 coital bleeding, pelvic pain and/or pressure symptoms then physical examination
4 and/or appropriate investigations should be undertaken to make a diagnosis. **[D**
5 **(GPP)]**

4.3 Physical examination

Physical examination of the woman by observation, abdominal palpation, visualisation of the cervix and bimanual (internal) examination has the purpose of detecting underlying pathology to inform treatment and need for investigation.

4.3.1 Review on physical examination for HMB

No evidence was identified relating to the physical examination of women who present with HMB. Therefore, this section was based on discussion within the GDG.

4.3.2 GDG interpretation of the evidence on physical examination

The GDG discussion focused on the benefits of physical examination. It was concluded that physical examination provided a useful tool for diagnosis of major pathology and indications for further investigations. The GDG stated that women should only go straight to investigations (except haematological investigations) without examination if they refuse examination or if it is not possible to undertake an examination. In addition, a general examination of paler may provide information on the presence of anaemia. The GDG highlighted that a general examination may be useful for identifying general medical conditions.

4.3.3 Evidence statement

No evidence was identified relating to the use of physical examination for HMB. Therefore, recommendations are based on the experience of GDG members.

1

2 **4.3.4 Recommendation on physical examination**

3 Physical examination should be undertaken prior to investigations (except
4 haematological investigations). **[D (GPP)]**

4.4 Laboratory tests in HMB

The measurement of the concentration of cells, corpuscles and chemical substances within blood can be used to detect illnesses that may cause or have been postulated as causing HMB. These tests are generally undertaken on venous blood.

4.4.1 Review on laboratory tests for HMB

Hormone testing

Epidemiological studies showed no link between hormone levels and HMB.^{145;146}

[EL = 2-; EL = 3] No studies were found on hormone testing for menorrhagia.

Thyroid function test

One case-control study (n = 428) showed no link between thyroid disorders and menstrual disturbances. Of the 214 women with thyroid disorders, 168 (78.5%) had regular menstrual cycles and 46 (21.5%) irregular cycles. Out of 214 normal controls, matched for age and weight, 196 (91.6%) had normal menstruation and 18 (8.4%) irregular cycles.¹⁴⁷ [EL = 2+]

Von Willebrand's

Two systematic reviews were identified that examined the prevalence of vWD in women with menorrhagia.

One review identified five studies and found prevalence of vWD to be between 5.3% to 20%.¹⁴⁸ [EL = 2-] A second review found a prevalence of 13% (95% CI 11 to 15.6%), with included studies reporting a range from 5% to 24%. Both the reviews

highlighted that differences in inclusion criteria may account for the wide differences in prevalence found.⁵³ [EL = 2+]

One additional study (n = 83) found that 11 of 59 (19%) were found to have coagulation disorder. 5 (45%) of 11 with coagulation disorders had life-threatening uterine blood loss. No subsequent studies were identified.¹⁴⁹ [EL = 2-]

The first review also examined the accuracy of vWD tests. Six studies found sensitivity of between 79% and 100%, and four studies showed a specificity range of 80% to 95%.¹⁴⁸ [EL = 2-]

Full Blood count

Six epidemiological studies and one systematic review were included in this section.

One epidemiological cohort study (n = 24894) undertaken in the USA showed that the prevalence of iron deficiency amongst the general population of women of menstrual age is approximately 11% compared to only 1% for men, and concludes that one likely explanation for this difference is menstruation.¹⁵⁰ [EL = 3]

A second epidemiological study (n = 748) showed that iron concentration decreased rapidly ($p < 0.01$) at greater than 80ml MBL.³⁰ [EL = 3]

A third study (n = 309) showed how all blood measures decreased with increased MBL. The figures show how haemoglobin, serum iron and serum ferritin levels are

changed by MBL: for <20ml (n = 130) = 13.3, 78.8, 28.5, respectively; for >80ml (n = 10) = 12, 47.3, 10.6, respectively. ¹⁵¹ [EL = 3]

A fourth study (n = 313) showed anaemia levels increased from 1.5% at an MBL of less than 20 ml to 10.3% for an MBL between 61 to 80ml and to 50% for an MBL between 161 and 240 ml. ³¹ [EL = 3]

A fifth study (n = 421) found the same association as the other studies, with the percentage of women with haemoglobin <12 g/dl and ferritin <16 ng/ml positively correlating with increased levels of MBL (MBL = <20ml (n = 48) then prevalence was 0%, MBL was 60 to 80 (n = 53) then prevalence was 17% and at MBL >100 ml (n = 46) there was a prevalence of 26.1%). ¹⁵² [EL = 3]

All these papers show that anaemia is an associated problem for people with HMB. In addition, given the correlation between MBL and anaemia, it is possible to use anaemia testing as a proxy for presence of HMB (where this is a presenting complaint). These studies show that MBL and iron deficiency anaemia are linked, with iron deficiency becoming a clinical problem at an MBL between 60 to 80ml MBL.

A high quality review identified 55 studies relating to testing for iron-deficiency anaemia. The study found that the serum ferritin test is the most accurate for diagnosing iron-deficiency anaemia, with a likelihood ratio of 51.85 at a level of <15 ug/l. No subsequent or additional studies were identified assessing the measurement of blood. No studies were included that examined how diagnosis of anaemia impacted on treatment of HMB. ¹⁵³ [EL = 2++]

4.4.2 Evidence statement for laboratory tests for HMB

Evidence shows that menstrual disorders are not associated with thyroid disease. Results from reviews and observational studies show prevalence of vWD and inherited blood disorders of 5% to 20% in women complaining of HMB. Evidence from a review suggests that accuracy of tests for vWD is variable. However, women with vWD and menorrhagia had identifiable risk factors, such as menorrhagia since menarche. Results from five epidemiological studies show that anaemia is associated with HMB. The studies show a positive correlation between increased MBL and full blood count measures. These studies show that prevalence of anaemia is high amongst those with clinically confirmed HMB (>80ml), with prevalence being greater 10% in this group. One review shows that serum ferritin testing is the most accurate method for confirming iron deficiency anaemia, with a likelihood ratio of a positive test of 51.85. However, there was no evidence that serum ferritin tests provided any more clinical information than a full blood count in relation to management of HMB.

4.4.3 GDG interpretation of evidence for laboratory tests

The GDG placed a high value of the cost-effectiveness and usability of any test. Discussion included input from a haematologist invited to provide expert opinion on the use of tests.

4.4.4 Recommendations on laboratory tests for HMB

A full blood count should be undertaken on women with suspected HMB. [C]

- 1 A serum ferritin test should not routinely be undertaken in women with HMB. **[B]**
- 2
- 3 Female hormone testing for women with HMB should not be performed. **[C]**
- 4
- 5 Thyroid testing in women with HMB should only be undertaken where other
- 6 symptoms of thyroid disease are present. **[C]**
- 7
- 8 Testing for coagulation disorders should only routinely be undertaken on women with
- 9 HMB in their teenage years or who have had HMB since menarche, and have other
- 10 personal or family history suggesting a coagulation disorder. **[C]**

4.5 Investigations for structural and histological abnormalities

Ultrasound scanning (US) and Magnetic resonance imaging (MRI) are techniques that obtain pictorial images of the structure of the human body without the use of ionising radiation. Saline ultrasonography involves the distension of the cavity of the uterus with salt water, introduced through the vagina in order to gain improved ultrasound images of the endometrium and endometrial cavity. These techniques can detect structural abnormalities but not histological abnormality.

Endometrial biopsy involves obtaining a piece of endometrium and subjecting it to histological analysis. The endometrium may be obtained during direct visualisation with a hysteroscope or blindly using a sampler (a plastic tube passed through the cervix which uses suction to obtain endometrium). The purpose is to detect the pre-malignant condition of endometrial hyperplasia with cytological atypia or endometrial carcinoma.

Dilatation and curettage is a procedure performed under general anaesthetic in which the lining of the uterus is blindly biopsied by scraping with an instrument. Endometrial sampling is a technique that also involves blind biopsy of the endometrium but does not require general anaesthesia. These techniques can only detect histological abnormality.

Hysteroscopy is an examination of the endometrial cavity and the surface of the endometrium using a hysteroscope. It can be combined with directed biopsy in

which the biopsy instrument is guided onto the area of concern under direct visualisation. It can thus be used to detect both histological and some structural abnormalities.

4.5.1 Review

Use of Ultrasound/sonography in menstrual disorders

Results from two systematic reviews and one subsequent RCT are reported in this section. The primary studies used in the reviews mainly involved abnormal uterine bleeding (AUB) populations (which included non-menstruating women with postmenopausal bleeding), rather than a menorrhagia specific population. Therefore, results have to be extrapolated for a menorrhagia population.

A systematic review examined the use of ultrasound, sonohysteroscopy and hysteroscopy in an AUB population. The review found a wide variation in published results on accuracy for each of the investigations. For transvaginal ultrasound (n = 10 studies) the range of sensitivity was 48% to 100% and for specificity the range was 12% to 100%, for identification of any intrauterine pathology. For sonohysteroscopy (n = 11) the range of sensitivity was 85% to 100%, and for specificity it was 50% to 100%, for identification of pathology. For hysteroscopy (n = 3) the range of sensitivity was 90% to 97% and for specificity it was 62% to 93%. The study concluded that all three methods were at least moderately accurate at identifying uterine pathology.¹⁵⁴ [EL = 2++] The second review also showed a range of results for the different investigations.¹⁵⁵ [EL = 2-]

One subsequent RCT (n = 683) undertaken in the UK was identified. The study used a pragmatic RCT design to examine combinations of imaging and biopsy to identify which were most effective at finding pathology in an AUB population. The study made no assumption that hysteroscopy was the 'gold standard' test on which to base results, therefore ultrasound and hysteroscopy were examined as equals. The study showed that ultrasound was successfully completed in 88% of cases compared to 77% for hysteroscopy. The study also showed that ultrasound identified more uterine fibroids than hysteroscopy (94 vs. 39) but fewer polyps (17 vs. 37). The accuracy of ultrasound for identifying endometrial cancer was calculated, the sensitivity was 66.7%, specificity 55.7%, PPV was 6.9% and NPV was 97%. In terms of acceptability, 11% found ultrasound 'unpleasant' compared to 27% and 29% for hysteroscopy and biopsy, respectively. The study concluded that ultrasound had both advantages and disadvantages over hysteroscopy.⁷¹ [EL = 1a]

A prospective cohort study (n = 223) undertaken in Turkey compared transvaginal ultrasound, hysteroscopy, saline infusion sonography using biopsy and D&C as reference methods. For TVS for identification of submucous fibroids compared to pathology: sensitivity = 58.3 specificity = 94.8, PPV = 46.7, NPV = 96.7, LR+ = 11.16, LR- = 0.44.¹⁵⁶ [EL = II]

Saline sonography

The results from the first review on saline sonography, is presented above.¹⁵⁴ The second review on saline contrast hysterosonography for AUB showed pooled sensitivity of 95% and specificity of 88% from 16 studies. The review concluded that SIS was an accurate method for investigation of uterine pathology.¹⁵⁷ {EL = 2++}

A prospective cohort study (n = 223) undertaken in Turkey compared transvaginal ultrasound, hysteroscopy, saline infusion sonography using biopsy and D&C as reference methods. For SIS for identification of submucous fibroids compared to pathology: sensitivity = 81.3, specificity = 98.0, PPV = 81.3, NPV = 98.0, LR+ = 40.35, LR- = 0.19. {25097} [EL = II]

Hysteroscopy

Results from two systematic reviews and one subsequent RCT are reported in this section. The results from the first review has been reported above.¹⁵⁴ A second review identified 65 primary papers on the use of hysteroscopy in endometrial disease. The review shows that hysteroscopy is accurate at identifying endometrial cancer (sensitivity = 86.4%, specificity = 99.2%), but less so at identifying endometrial disease (sensitivity = 78%; specificity = 95.8%).¹⁵⁸ [EL = 2++]

A subsequent RCT (n = 683) on women with DUB compared ultrasound and hysteroscopy (both with and without biopsy). The study shows that hysteroscopy was undertaken successfully in 77% of cases. The trial also found that ultrasound was more accurate at identifying uterine fibroids than hysteroscopy (84 vs. 39), though hysteroscopy was better at identifying polyps (13 vs. 37). The trial found hysteroscopy has a sensitivity and specificity for identifying endometrial cancer of 20% (95% CI 3.6 to 62.4) and 98.8% (95% CI 96.5 to 99.6), respectively.⁷¹ [EL = 1a]

A subsequent RCT (n = 83) on women referred for hysteroscopic assessment compared a rigid against a flexible hysteroscope. The study found that the flexible

hysteroscope resulted in less pain and discomfort for the women during and after the procedure.¹⁵⁹ [EL = 1b]

A prospective cohort study (n = 223) undertaken in Turkey compared transvaginal ultrasound, hysteroscopy, saline infusion sonography using biopsy and D&C as reference methods. For hysteroscopy for identification of submucous fibroids compared to pathology: sensitivity = 90.9 specificity = 95.8, PPV = 76.9, NPV = 98.6, LR+ = 21.67, LR- = 0.10.¹⁵⁶ [EL = II]

Additional information on imaging techniques can be found in the evidence table.
72;74;80;81;86;87;160-215;215-217

Use of MRI in menstrual disorders

One cohort study (n = 119) compared use of MRI and ultrasound for identification of adenomyosis. There was no statistical difference between sensitivities (p = 0.65) and specificities (p = 0.75) of the test. No other studies were found relating to MRI and HMB or HMB related conditions.²⁰⁵ [EL = Ib]

Endometrial biopsy

A number of biopsy methods are available; however, the most often tested in menstrual problems is the Pipelle curettage tool.

One diagnostic RCT (n = 683) showed success rates for completion of biopsy of between 84% and 80% depending on method and patient population. The sensitivity, specificity, PPV and PNV of biopsies for identifying endometrial cancer

were, respectively: for Pipelle (n=473) 70%, 100 %, 100% and 99.4%; and for Tao brush (n=478) 90%, 100%, 100% and 99.8%. ⁷¹ [EL = 1a]

A diagnostic study (n=275) on women with AUB compared two biopsy techniques and found a failure of 12 (9.5%) for the Novak method versus 19 (12.8) for the Pipelle group. ⁷⁸ [EL = Ia]

A diagnostic study [n=102] comparing ultrasound with biopsy for identification of adenomyosis found that needle biopsy identified 16 cases of which 13 were confirmed and it missed 16 cases. The sensitivity, specificity, PPV and PNV of biopsies for identifying adenomyosis were, respectively: 44.8%, 95.9%, 81.2%, 81.4%. ⁸¹ [EL = Ib]

A diagnostic study (n=269) on women with AUB, found 154 of 170 (90.6%) samples provided by Pipelle biopsy gave enough information for histology, compared to 66 of 97 (68%) of D&C's (p<0.0001 for difference). ²¹⁸ [EL = II]

A diagnostic study (n=114) examining the Pipelle biopsy, found that in 62 (54.4%) cases, adequate material for histology was retrieved. ²¹⁹ [EL = III]

A diagnostic study (n=276) on women with AUB compared biopsy with D&C results, and found that 220 of 265 of the biopsy and D&C results were the same. Furthermore, in 44 cases (16%) biopsy provided improved results, but in 9 cases (3%) biopsy provided reduced results. ²²⁰ [EL = III]

A diagnostic study (n=37) on women with AUB undertook biopsies of 37 women with known endometrial carcinoma, and found that 25 (67%) of 37 biopsy samples were positive for endometrial cancer.²²¹ [EL = II]

A diagnostic study (n = 2586) on a sample of women from the general public compared two biopsy methods. The study found that Mi-Mark was successful in 1117 (86.39%) of cases, and Isaac was successful in 1194 (92.34%) of cases ($P < 0.001$).²²² [EL = III]

Economic Evidence

No studies of MRI, ultrasound, saline-infused sonography, hysteroscopy, biopsy or visualisation and biopsy that met the inclusion criteria for economic evidence were identified in the review. In consultation with the GDG, a decision analytic model was developed to examine the cost-effectiveness of three of these imaging techniques (see Appendix A for full details). The model showed that ultrasound was more accurate and less costly than either saline-infused sonography or hysteroscopy. For a cohort of 1000 patients examined for the presence of structural abnormalities, ultrasound generated 810 correct diagnoses at a cost of £107,490 compared with 735 correct diagnoses at a cost of £145,110 using saline-infused sonography and 696 correct diagnoses at a cost of £209,720 using hysteroscopy.

Visualisation and biopsy

One sub-area to emerge from the review was the use of ultrasound in combination with biopsy, with three studies examining this.

One large trial (n = 683) showed that ultrasound and biopsy complemented one another in terms of identification of pathology. However, use of combined methods meant accepting a lower overall 'success' rate, with ultrasound and Pipelle being completed 60% of the time.⁷¹ [EL = 1a]

A diagnostic trial (n=411) involving women with menorrhagia, compared ultrasound and Pipelle against hysteroscopy alone, and found that 14 benign lesions (18%) were missed by the combination (p = 0.0076), but 2 hyperplasia and 1 carcinoma were detected, that were not found on hysteroscopy. Furthermore, ultrasound and biopsy were associated with less pain and higher acceptability than hysteroscopy.²²³

[EL = 1b]

A diagnostic study (n = 377) showed that combined hysteroscopy and biopsy made no difference to management options, compared to biopsy results alone. This has implications for the use of a test, as if a test result has no influence on management plans then there is no benefit in using that test.²²⁴ [EL = 1b]

A diagnostic study (n=78) showed that a combination ultrasound and Pipelle biopsy may provide more robust assessment than using the investigations separately.¹⁸³

[EL = II]

A systematic review (n = 39 studies) examined the use of endometrial sampling for identification of carcinoma and hyperplasia. For identification of carcinoma the study calculated sample size-weight combined sensitivities were 68%, 78%, and 81% where hysterectomy, D&C or both were, respectively, used as reference method.

The specificities were 99.7%, 99.6% and 99.9%, respectively. For identification of Atypical hyperplasia the study calculated sample size-weight combined sensitivities for identification of hyperplasia, were 74%, 75%, and 45% where hysterectomy, D&C or both were, respectively, used as reference method. The specificities were 100%, 99.1% and 100%, respectively.²²⁵ [EL = II]

4.5.2 Evidence statement on investigations for HMB

Evidence shows that MRI has no advantage over ultrasound as a first-line investigation for HMB, but may be reserved for problem solving where ultrasound provides indeterminate results. Evidence from two reviews show that ultrasound is an accurate method for identifying pathology (sensitivity 48% to 100%, and specificity 12% to 100%). Furthermore, studies show that ultrasound is better at identifying fibroids than hysteroscopy, but is less accurate for identifying polyps or endometrial disease when compared with hysteroscopy. However, it is associated with higher completion rates (88%) and greater acceptability (11% finding it 'unpleasant') with women than hysteroscopy (77% and 27%, respectively). Saline sonography is an accurate method for identification of pathology, the range of sensitivity was 85% to 100% and for specificity it was 50% to 100%. One review shows that for hysteroscopy the range of sensitivity was 90% to 97%, and for specificity it was 62% to 93%. Economic modelling for this guideline (Appendix A) showed that ultrasound is more accurate and less costly than the other imaging methods examined (hysteroscopy and saline-infused sonography).

Eight studies found that biopsies had a successful completion rate of between 54.4% and 93%. The sensitivity of tests varied between 70 to 100%, but specificity was

100%. Use of ultrasound and biopsy in combination, has completion rates of 60%, and is associated with improved identification of endometrial disease compared to hysteroscopy alone. No evidence was found on the population risk of endometrial cancer of women seen in secondary care for HMB.

4.5.3 GDG interpretation of evidence on investigations for HMB

The GDG placed a high value on cost-effectiveness and usability when interpreting the evidence.

The GDG recognised that different investigative methods were better for identifying certain types of pathology than others. The GDG focused upon the need to identify uterine fibroids, as these are linked to HMB (Section 3.5) and pre-malignant or malignant pathology, as identification of life-threatening pathology is essential.

4.5.4 Recommendations on investigations for HMB

Ultrasound should be considered the first line diagnostic tool for the identification of structural pathology in HMB. [A]

Hysteroscopy with biopsy is an accurate method for identification of endometrial and some submucosal pathology, but should be considered only where ultrasound outcomes are inconclusive. [A]

1 An endometrial biopsy should be taken if the woman has persistent intermenstrual
2 bleeding, is aged 45 years and over and has declined or failed adequate medical
3 treatment, and before undertaking surgery or UAE procedures. **[D(GPP)]**

4
5 Saline Infusion Sonography should not be undertaken as a first-line investigation of
6 HMB. **[A]**

7
8 MRI scanning should not be used as a first line diagnostic tool for HMB. **[B]**

9
10 D&C should not be used as a diagnostic tool for HMB. **[B]**

11
12 If a women has fibroids that are intracavitary or a uterine length greater than 12cm
13 then referral for specialist opinion should be offered **[D(GPP)]**

14 **4.5.5 Research Recommendations**

15 The production of predictive values for HMB and significant uterine pathology in
16 primary care populations.

5 Education, Information Provision, Patient Choice and Lifestyle Interventions

5.2 Introduction

Education and information provision, patient choice and patient empowerment are increasingly important in modern healthcare. The rationale for addressing these concepts are that they:

- Lead to more ethical decision-making, as woman with HMB can be enabled to play an active and informed role in decision-making.
- Allow the woman with HMB to maximise the benefit of available treatment as decisions are based on informed choice, so the woman in partnership with the clinician can choose the treatment that they feel will give them the best overall outcome.
- Improve satisfaction with treatment for women with HMB, as they understand the risks and benefits involved, and have been active in the decision-making process.
- Improve adherence with treatment, as the woman has been involved in the decision-making and understands why a treatment regimen is needed;
- Allow greater autonomy and self-management for the woman, as she understands the condition and treatment.

5.3 Education, information provision and counselling for women with HMB

Patient education and information provision provide the cornerstones of modern healthcare. They are essential for patient empowerment, ethical and legal treatment provision, informed choice, informed consent and shared-decision making.^{226;227} A number of basic toolkits are available to help produce patient information and education resources.²²⁸ Providing appropriate patient education and information allows women to make informed decisions about what treatment is right for them, and so allows them to maximise the benefit for themselves from a treatment plan. However, there are currently concerns about the provision of information for women with HMB or undergoing HMB related treatments.²²⁹

5.3.1 Education and information provision of women with HMB

Nine observational or descriptive studies were identified that highlight the issues that are important to women with regards to the provision of information and the content of that information provision.

A study (n = 30) used qualitative interviews to investigate women's experience of hysterectomy. The main themes to emerge from the study identified were:

1) Fear for sexual identity and relationship with partners before surgery; 2) freedom from pain and embarrassment; 3) Improved sexuality and self-esteem after surgery.

²³⁰ [EL = 3]

A study (n = 10) using qualitative interviews, examined the decision-making process that women go through before having a hysterectomy. The authors outline a model

1 containing four phases of decision-making: 1) Seeking solutions - finding information
2 on symptoms that occur via friends and family, clinicians etc; 2) Hold on - changing
3 lifestyle in order to cope with symptoms; 3) Changing course - single event usually
4 triggering women to seek a solution to the problem; 4) Taking charge - is the time
5 when the women organises and prepares for the hysterectomy. This model is useful
6 as it highlights where in the decision-making process women will need information.

7 ²³¹ [EL = 3]

8
9 A study (n = 29) used qualitative interviews to investigate women's experience of
10 hysterectomy. The study found that most women delayed seeking formal medical
11 help for as long as possible, often using complementary therapy. The study found
12 that women often tried to get information about their condition as early as possible
13 from various sources. Furthermore, the study found that women received a lot of
14 information about hysterectomy from clinicians, but little information on alternatives.
15 Women stated that they had a hysterectomy based upon the advice of the
16 gynaecologist, but that they were often told to think about the impact it would have
17 and to delay the operation if they had serious social or psychological concerns with
18 it. The study also highlighted that women were often still undecided after they
19 agreed to surgery. Women also said that they were told to talk to family and friends
20 about the procedure before making a decision. ²³¹ [EL = 3]

21
22 A study (n = 50) used qualitative interviews to examine women's experience of
23 hysterectomy. The main factors it identified were: 1) A lack of information provision
24 about the nature and the implications of hysterectomy. 2) Most women were afraid

of having major surgery. 3) Women highlighted the need for support networks. 4) A lack of information during the recovery phase.²³² [EL = 3]

These qualitative studies highlight areas of concern and the information requirements of women facing hysterectomy. The main themes appear to be fear of hysterectomy and the physical, social and psychological impact it could have. It appeared that women wanted information on these issues in order to help them with the decision-making process.

A study (n = 102) quantitatively surveyed women's opinion of hysterectomy. It identified seven major themes: 1) Positive aspects - 61 of 102 outlined positive aspects of treatment by hysterectomy, including relief from symptoms, accurate information, supportive physician, involvement in decision-making. 2) HRT - fears and concerns about using HRT, based on lack of information. 3) Insufficient information - 38 of 102 thought insufficient information had been given about hysterectomy and the physical impact it would have. 4) Sexual concerns - 28 of 102 were concerned about changes caused by hysterectomy and lack of information about this. 5) Structure of emotional support - 20 of 102 outlined the need for systems to provide emotional and informational support for women. 6) Psychological sequelae - 17 of 102 talked about psychological distress caused by hysterectomy, including mood swings etc. 7) Feelings of loss - 5 of 102 wrote about loss of femininity caused by hysterectomy, and the feeling of grief this caused.²³³ [EL = 3]

A study (n = 148) from the USA used a survey to examine women's experience of hysterectomy. Four main themes emerged: 1) The outcomes of hysterectomy:

1 Women identified the benefit of the relief from symptoms as a result of hysterectomy.
2 Women also wanted minimally invasive surgery and quick recovery in order to return
3 to work and family responsibilities. Women were concerned about the side-effects of
4 surgery, both physical and emotional. 2) The decision to have surgery: women
5 consulted friends and family about the decision to have a hysterectomy, often using
6 others experience as a guide. Women wanted to have a clear rationale for having
7 surgery from clinicians. 3) Women were also concerned about the loss of sexuality
8 and the male response to hysterectomy. 4) Opinions on healthcare - women felt that
9 clinicians were only interested in financial gain from doing a hysterectomy. Women
10 wanted female doctors as they thought they were less likely to suggest a
11 hysterectomy. The survey results correlate with the findings of the qualitative
12 studies, with women's concerns and fears about hysterectomy, and its psycho-social
13 impacts, being highlighted.²³⁴ [EL = 3]

14
15 A study (n = 10) which surveyed women's information requirements prior to
16 hysterectomy, outlined five elements that needed to be included: 1) Advantages of
17 hysterectomy, 2) Possible risks and side-effects of hysterectomy, 3) Treatments
18 available other than hysterectomy, 4) Advantages of treatments other than
19 hysterectomy, and 5) Disadvantages of treatments other than hysterectomy. The
20 study found that women felt that not enough information about the risks and
21 disadvantages of surgery was provided prior to surgery. The study also highlighted
22 that women sought information in addition to the information provided by clinicians,
23 for a number of reasons. The information sought included: what hysterectomy
24 involves, what effect hysterectomy has on the menstrual system, other effects of
25 hysterectomy, what other treatment options would involve, what effect other

treatments would have on period problems and what they may need to take after the hysterectomy. When asked questions about whether the doctor had been supportive during the decision-making process, between 15% to 30% were neutral or dissatisfied. When asked questions about whether hysterectomy was the right decision, approximately 10% of women were neutral or disagreed.²³⁵ [EL = 3]

One study was identified that examined a decision-making support system for women facing hysterectomy. It identified nine elements in counselling women about hysterectomy: 1) Perceptions of decision - knowledge, expectations, values, decisional conflicts, stage of decision making, predisposition towards options. 2) Perceptions of others - support, pressures and roles in decision making. 3) Resources to make decision - personal (skills, motivation, self-confidence, previous experience), external support networks. 4) Provide decision support: provide information - health situation, options, outcomes, other opinions and choices. 5) Re-align expectations of outcomes. 6) Clarify personal values for outcomes. 7) Provide guidance and coaching - steps in decision-making, communicating with others, handling pressure, accessing support and resources. 8) Evaluate: Decision-making - reduce decisional conflict, improve knowledge, realistic expectations, clear values, congruence between values and choice, implementation of chosen option, self-confidence and satisfaction with decision-making. 9) Outcomes of decision: Persistence with others, improved quality of life, reduced distress, reduced regret, informed use of resources.²³⁶ [EL = 4]

A study (n = 38) from the USA, that surveyed women's experience of hysterectomy, identified three main themes: decision-making about hysterectomy; outcome of hysterectomy; perceptions of the male response to hysterectomy.²³⁷ [EL = 3]

5.3.2 Review of education for women with HMB

Overview of available evidence

One systematic review of decision aids (across all conditions), five RCTs and one economic analysis were identified. It is recognised that a vast amount of literature exists on patient education and information provisions that is non-specific to HMB, and that has not be reviewed here.

Education for women with HMB

One systematic review was identified that examined the use of decision aids across all conditions. The results from the systematic review showed that they improve patient knowledge, help patients form a clear preference and aid patients in taking part in decision making. Among the trials comparing decision aids to usual care, decision aids performed better in terms of: a) greater knowledge (WMD 18.75 of 100 [95% CI 13.14 to 24.35]); b) more realistic expectations (RR 1.4, [95% CI: 1.1 to 1.9]); c) lower decisional conflict related to feeling informed (WMD -9.1 of 100, [95% CI: -12 to -6]); d) increased proportion of patients that controlled decision making (RR 1.49 95% CI 0.99, 2.25); e) reduced practitioner controlled decision-making (RR = 0.68 [95% CI 0.53, 0.89]), and f) reduced proportion of people who remained undecided post intervention (RR = 0.43 [95% CI 0.27, 0.70]). When simpler decision aids were compared to more detailed decision aids, the relative improvement was significantly better for the more detailed tools, for: a) knowledge (WMD 4 out of 100 [95% CI: 3 to 6]); b) more realistic expectations (RR 1.5 [95% CI: 1.3 to 1.7]); and c) greater agreement between values and choice. Decision aids appeared to do no better than usual care in affecting satisfaction with decision

making, anxiety and health outcomes. Decision aids had no consistent effect on which healthcare options were selected. The heterogeneity of the studies included in the review mean that it is difficult to compare other outcomes, such as physical or psychological outcomes. In addition, the systematic review covered decision aids used across all conditions so the applicability to HMB is unknown.²³⁸ [EL = 1+]

One RCT (n = 894) undertaken in the UK compared providing no information, an information booklet, and an information booklet plus an interview to elicit women's preferences. This study was included in the systematic review of decision aids outlined above, but is summarised here because it specifically examines education for women with menorrhagia. The study found that those in the intervention groups (booklet only or booklet and interview) were more likely to have treatment preferences than those in the control group (no information) at follow-up (booklet only [OR 95% CI 1.46 to 4.20] and booklet and interview [OR 95% CI 1.72 to 5.13]). In addition, they were also more likely to feel involved in decision making than the control group (booklet only group [OR 95% CI 1.04 to 1.86] and booklet and interview group [OR 95% CI 0.99 to 2.25]), more likely to get their preferred treatment than the control group (booklet only group [OR 95% CI 1.20 to 2.97], and booklet and interview group [OR 95% CI 0.62 to 2.01]), and more likely to be satisfied with treatment than the control group. However, there was no difference between groups in terms of quality of life, as measured on SF-36 and EQ-5D scales. Furthermore, there was no difference between groups in terms of perceived involvement in treatment choice.²³⁹ [EL = 1+]

1 A second RCT (n = 569) undertaken in Finland examined the use of an information
 2 booklet on HMB against no information or usual care. The study found more women
 3 in the information group had a treatment preference after they had received the
 4 booklet than those in the control group (4% versus 11% had made no treatment
 5 decision by 3-months). However, there was no statistical difference between the
 6 groups in level of knowledge, satisfaction with clinic or anxiety. There were also no
 7 differences between groups on the SF-36 scores, VAS perceived health, anxiety and
 8 psychosomatic symptoms, menstrual symptoms, sexuality, satisfaction with
 9 treatment except for the emotional role on SF-36 (p = 0.01), where the intervention
 10 group improved more. However, scores for both intervention and control groups
 11 significantly improved from baseline to follow-up, except for sexuality scores. There
 12 were no statistically significant differences between the groups in terms of health
 13 service use or cost. The study concluded that the information booklet was of limited
 14 use.²⁴⁰⁻²⁴² [EL = 1-]

16 A third randomised study (n = 40) examined if differences occurred when women
 17 were provided with standard information or specific risk of treatment information.
 18 The study found no difference between groups for anxiety, but significant difference
 19 for knowledge (p = 0.002) and satisfaction (p < 0.001) in favour of the specific
 20 information group.²⁴³ [EL = 1-]

22 A fourth randomised study (n = 60) examined use of a cognitive support method in
 23 women scheduled for hysterectomy. The study found that women in the cognitive
 24 group had less worries, but less knowledge than the information group prior to
 25 surgery, and that both groups had less anxiety, less worries and better knowledge

than the control group. Post-operatively, the study found that the cognitive group had fewer symptoms, and fewer days of pain than the information group.²⁴⁴ [EL = 1-]

A fifth randomised study (n = 96) examined cognitive training prior to surgery versus a standard information provision. The study found that anxiety scores (60.17 (SD 6.56) vs. 62.77 (SD 5.77), $p < 0.05$), pain scores (cognitive = 7.10 (SD 0.72) vs. information = 7.35 (SD 0.56), $p < 0.05$) and patient satisfaction (cognitive = 47.38 (SD 3.89) vs. information = 45.75 (SD 3.52), $p < 0.05$) all favoured the cognitive group. No difference in analgesic use was reported.²⁴⁵ [EL = 1-]

Economic papers

One economic evaluation (n = 894) met the criteria for inclusion, assessing the cost-effectiveness of no information, an information booklet, and an information booklet plus an interview to assess preferences of women with menorrhagia. The economic evaluation was conducted in conjunction with the trial, and in the base case analysis, all health service contact costs during the trial were measured for each woman. Overall, both intervention groups showed lower mean costs [information alone, £1333; interview plus information, £1030] and higher mean quality adjusted life years [1.567 and 1.582] compared with the control group [£1810, 1.574]. The information plus interview intervention is dominant having both the lowest mean cost, and giving higher mean quality adjusted life years. Overall costs are sensitive to the costs associated with health service contacts, the costs of the interventions themselves and the perceived increase in consultation length. When unrelated health service contact costs (non-gynaecology outpatient and GP appointments) are excluded from the analysis, information plus interview is still the dominant intervention when compared with either the information alone or control groups. There is no difference

in mean quality adjusted life years from the base-case analysis, and the mean costs for the interview group (£907) remain lower than for the control (£1446) or the information only group (£995). In addition, when all inpatient and unrelated costs are excluded from the analysis, the information plus interview intervention is still dominant, with lower mean costs [£853] than either information alone [£946] or the control [£887]. Again, there is no difference in the mean quality adjusted life years between this analysis and the base-case.²³⁹ [EL = 1+]

5.3.3 Evidence statement on education for women with HMB

A systematic review showed that decision aids, across all diseases, reduced the proportion of people who remained undecided post intervention (RR = 0.43 [95% CI 0.27 to 0.70], but was unable to show that decision aids improved patient outcome due to the heterogeneity of studies.

Three RCTs examined education provision for women, these found that education improved knowledge and women being able to make treatment decisions, but had no effect on patient outcome. Two small randomised studies of cognitive training prior to surgery showed that this reduced anxiety and improved outcome. One economic study shows that providing information to women in conjunction with a structured interview with a nurse, designed to elicit preferences, is cost-effective. It is less costly and results in more quality adjusted life years than either information alone or standard practice.

5.3.4 GDG Interpretation of evidence on education for women with HMB

The GDG placed a high value on the need for education and an information provision for women with HMB.

The GDG discussion focused on:

- the need for clinicians to be aware that unwillingness (women do not want to express their thoughts and feelings to clinicians), inability (women do not know how to express their thoughts and feelings to clinicians) and ambivalence (women have no motivation to express self to clinicians) are all factors that can have an impact upon the information and education needs of women.
- Clinicians should be able to refer a woman to any source of information that is felt to provide in-depth, reputable and reliable information support, on a subject.
- Clinicians should be aware that not only the content of education is important, but also where it is provided, by whom it is provided and in what form it is provided.
- Clinicians should be aware that education should extend beyond treatment options.

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5.4 Patient Choice

Decision-making in modern medicine is based around the concept of shared-decision making, which involves the clinician and patient in partnership, forming a decision about which management strategy best meets the patients overall needs. Shared-decision making involves a formal recognition that clinicians hold expert knowledge of disease management, which the patient should have access to, and that the patient has intimate knowledge about the impact of the condition and their needs from any treatment. However, shared decision-making is not possible in situations where: 1) Paternalistic decision-making happens - where the clinician imposes the treatment they feel is best on the patient. 2) Consumerist decision-making - where a patient demands a treatment against clinician advice. 3) Where the clinician and/or patient does not feel they have the knowledge or expertise to take part in shared decision-making.

A number of factors are likely to influence patient and clinician decision-making processes, and sociological and psychological models are available to help explain the processes involved.

5.4.1 Review on patient choice

Overview of available evidence

No review was scheduled for this question, as it was based purely on discussion amongst the GDG, however the GDG did use references to help their discussion.

242;246-258

5.4.2 Evidence statement on patient choice

No evidence specific to women with HMB was identified in relation to patient choice.

5.4.3 GDG discussion on patient choice

The recommendations made on patient choice were based upon a discussion within the GDG. No formal review of evidence was undertaken for this question, though supporting literature was provided. The main discussion points highlighted by the GDG were the following:

- Clinicians and women should be aware that women's ambivalence and clinician uncertainty about optimal treatment can affect the decision making process and patient choice. Women's ambivalence relates to them having no clear preference or desire to make a choice, with the result that women often defer to clinicians choice. This is recognised in research, and is an area of concern in shared decision-making, as the clinician has to be prepared if the woman wants them to make the decision.²⁵⁹ Clinician uncertainty or equipoise relates to them having no preference for one treatment over another. This means that the final choice would be based purely on women's preference. If a woman's ambivalence and clinician equipoise exist at the same time then shared-decision making could be hampered. Therefore, it must be recognised that patient choice and shared decision-making are complex issues, involving patient and clinician factors.
- It should be recognised that while women may make a decision about a treatment they can be ambivalent about that decision. The consequences of any such treatment can have long-term mental health impacts. This has to be

considered when the women are making an irreversible decision, as counselling, information and education may help women to recognise their ambivalence and use it to make highly personal treatment choice.

- It is essential that clinicians should not be forced into making a decision where they consider that the risks of treatment considerably exceed any benefits.
- Time should be taken to identify the patient's understanding and expectations from any treatment, as these will effect satisfaction. If the clinician and woman can agree on an expected outcome, then a management strategy can developed to best achieve these results.
- The issue of equity and equality of access to care have to be considered in relation of patient choice. Whilst many women have the ability and skills to make informed choices, it is important that all women are given an equal opportunity to be involved in decision making. In particular, women with special needs or whose first language is not English and/or whose cultural background is not based around consumer choice, may need specialist support in making to an informed decision.

5.4.4 Recommendations on education and choice for women with HMB

Patients referred to secondary care with menorrhagia should be provided with an information pack prior to their outpatient appointment. **[A]**

Where a potential treatment involves the loss of fertility then counselling and support should be made available to the woman to the woman throughout the care pathway.

[D(GPP)]

1 A woman with HMB should be given the opportunity to review and veto any
2 treatment decision. **[D(GPP)]**

4 Patients should be allowed choice of treatment, but within the clinicians' remit of
5 balancing risk and benefits based on evidence and their competence. **[D(GPP)]**

7 A woman with HMB must have the option of gaining a second medical opinion where
8 a clinician has no knowledge or opinions are at odds. **[D(GPP)]**

10 A woman with HMB should have adequate time and support in the decision making
11 process, especially where the treatment decision has irreversible results. **[D(GPP)]**

13 Where a potential treatment involves the loss of fertility then counselling and support
14 should be made available to the woman throughout the care pathway. **[D(GPP)]**

15 **5.4.5 Implementation advice on improving choice and education for** 16 **women with HMB.**

17 The following section provides advice on improving patient choice, information
18 provision, communication and education. The advice provided in this section is seen
19 as fundamentally important to the successful provision of healthcare, and is seen a
20 prerequisite for the implementation of the recommendations outlined in the rest of
21 the guideline. The reason that these issues have not recommendations is that they
22 represent generic issues.

24 The GDG believe that the following set of principles should be followed when treating
25 women with HMB:

- 1 ▪ Treatment decision-making should involve negotiated agreement between the
- 2 woman and the clinician.
- 3 ▪ Women should be allowed choice of treatment, but within the clinicians' remit
- 4 of balancing risk /benefits analysis.
- 5 ▪ Clinicians should elicit women's preferences and outcomes, help women
- 6 express concerns about treatment options and, as a result, devise an
- 7 individualised treatment plan.
- 8 ▪ Both clinicians and women should be aware that when there is women's
- 9 ambivalence and/or clinician uncertainty about optimal treatment, that this
- 10 may affect the shared-decision making process.
- 11 ▪ Women must have adequate time and support in the decision making
- 12 process, especially where the treatment decision has irreversible results.
- 13 ▪ The woman must be given the opportunity to review any treatment decision.
- 14 ▪ Women must have the option of gaining a second medical opinion where a
- 15 clinician has no knowledge or opinions are at odds.
- 16 ▪ The woman has the right to veto any treatment decision.
- 17 ▪ Where a potential treatment involves the loss of fertility, then appropriate
- 18 counselling and support should be made available to the woman.
- 19 ▪ When no treatment is felt to be required then the women must be reassured.
- 20 This should involve a clear explanation for the decision and identifying why
- 21 the woman has sought help and then reassuring on these issues.
- 22 ▪ Clinicians need training about maximising equality and equity of patient
- 23 choice, and in how to provide emotional and psychological support as part of
- 24 the consultation process.
- 25

Practitioners should aim to be holistic in terms of education for women with HMB by including as a minimum data set:

- Information on the condition (including prognosis and epidemiology).
- Anticipated outcome in terms of treatment success rates and recovery.
- Average duration and recovery time from procedures.
- Likelihood of adverse events or complications occurring with particular intervention.
- Likelihood that additional treatment will be required after a particular intervention.
- Absolute risks and benefits of the range of treatments.
- List of health care providers offering relevant treatments for HMB.
- Potential wider social and psychological impacts of any treatments.
- Competencies required by clinicians for the relevant treatment options.
- Sources of further information/advice, including sources outside the NHS.

A key issue in provision of patient information is the formatting of this information. It is suggested that standardised criteria, such as those outlined on the DISCERN instrument are used. The DISCERN criteria for writing patient information leaflets are:

1. Are the aims clear?
2. Does it achieve its aims?
3. Is it relevant?
4. Is it clear which sources of information were used to compile the publication (other than the author or producer)?
5. Is it clear when the information used or reported in the publication was produced?

- 1 6. Is it balanced and unbiased?
- 2 7. Does it provide details of additional sources of support and information?
- 3 8. Does it refer to areas of uncertainty?
- 4 9. Does it describe how each treatment works?
- 5 10. Does it describe the benefits of each treatment?
- 6 11. Does it describe the risks of each treatment?
- 7 12. Does it describe what would happen if no treatment is used?
- 8 13. Does it describe how the treatment choices affect overall quality of life?
- 9 14. Is it clear that there may be more than one possible treatment choice?
- 10 15. Does it provide support for shared decision-making?
- 11 16. Based on the answers to all of the above questions, rate the overall quality of the
- 12 publication as a source of information about treatment choices
- 13
- 14
- 15

5.5 Lifestyle interventions for HMB

5.5.1 Introduction on lifestyle interventions

Lifestyle interventions and indications are often promoted as ways to manage chronic conditions. Lifestyle interventions are changes to the daily activities of an individual that help reduce symptoms or reduce the impact of symptoms. Examples of lifestyle interventions include diet and exercise.

5.5.2 Review on lifestyle interventions

Overview of available evidence

No studies were identified on lifestyle indications or interventions for the management of HMB. Studies have been identified linked to risk factors, such as smoking and obesity, however these are not seen as planned interventions but as general health promotion issues.

5.5.3 Evidence statement on lifestyle interventions

No evidence was identified

6 Hormonal treatment for HMB

HMB can occur for a variety of reasons. Many women with HMB will experience ovulatory (generally regular) cycles. In these women, their excessive bleeding may not be attributable directly to a hormonal imbalance but to a disturbance of the physiological pathway e.g. increased fibrinolytic activity in the endometrium, increased prostaglandin levels or the presence of fibroids.

In women with HMB related to hormone imbalance, there is often no recognisable pathology; their bleeding results from abnormalities in the hypothalamo-pituitary-ovarian-endometrial axis. This results in anovulatory (generally irregular) cycles which are particularly common at the time of menarche and around the perimenopause. Other less common but more specific causes are polycystic ovaries, hypothyroidism and gross obesity. The failure of ovulation and progesterone induced luteal phase secretory transformation of the endometrium, results in bleeding that is often heavy, less clearly defined and irregular.

Figure 7.1 shows a schematic of all the RCT comparisons that have been undertaken for pharmaceutical treatments. What this figure highlights is the variable amount of RCT evidence available, comparing each treatment.

6.2 Intrauterine levonorgestrel-releasing systems (LNG-IUS)

The Levonorgestrel intrauterine - releasing system (LNG-IUS) is an intrauterine, long term progestogen only method of contraception licensed for five years of use. It has a T-shaped plastic frame with a rate limiting membrane on the vertical stem releasing a daily dose of 20ug of levonorgestrel. The effects of the LNG-IUS are local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus and suppression of ovulation in a small minority of women. The system has to be fitted and removed by a qualified practitioner. As well as being licensed as a contraceptive device, the IUS is also licensed for the management of idiopathic menorrhagia and as the progestogen component of an HRT regime.

6.2.1 Review on LNG-IUS

Overview of available evidence

Two reviews^{260;261} were identified

LNG-IUS

A systematic review from 2005 identified 10 RCTs comparing LNG-IUS with surgery or pharmaceutical treatments.²⁶⁰ When comparing LNG-IUS against any pharmaceutical treatment the review calculated the OR for amenorrhoea (greater than three months) (1 RCT, n = 35) was 8.67 [95% CI 1.52, 49.35] in favour of LNG-IUS. The OR for proportion unwilling to continue with treatment (n = 91) OR 0.27 [95% CI 0.10 to 0.67] in favour of LNG-IUS. The OR for proportion of women satisfied with treatment (1 RCT, n = 40) was 2.13 [95% CI 0.62 to 7.33]

When comparing LNG-IUS against endometrial ablation the review calculated the OR for the proportion of women satisfied with treatment (n = 136) was 0.61 [95%

0.26 to 1.46] . The OR for amenorrhoea at up to 12 months (n = 223) was OR 0.75 [95% CI 0.36 to 1.54] in favour of surgery. The WMD for PBAC score at 12 months (1 RCT, n = 66) was 33.20 ml [95% CI 27.16 to 39.24] in favour of ablation.

When comparing LNG-IUS against hysterectomy the study calculated OR for satisfaction with treatment (n = 232) as being 1.17 [95% CI 0.41 to 3.34] in favour of hysterectomy.²⁶⁰ [EL = 1++]

In the second review ten studies met the inclusion criteria. This consisted of five RCTs and five case-series. The study did not perform a meta-analysis, but reported individual trial outcomes. The MBL reductions reported in the RCTs were between 71% and 96%.²⁶¹ [EL = 1+]

Information from the individual RCTs included in the reviews can be found in the evidence table.^{106;107;262-272}

6.2.2 Health economics

One trial conducted in Finland and reported in US Dollars compared LNG-IUS with hysterectomy. The LNG-IUS was found to be cost-effective at five years when compared with hysterectomy. There was no statistically significant difference in quality of life scores at five years, as measured by the EQ-5D instrument, between the two treatment groups. Mean direct costs in the LNG-IUS arm remained significantly lower (\$1892) than the hysterectomy arm, (\$2787) despite 40% of women in the LNG-IUS arm going on to have a hysterectomy. The trial did not compare the LNG-IUS with other medical treatments (see Appendix A).¹⁰⁶

No UK based comparisons of LNG-IUS with any other medical or surgical treatment strategies were identified as a part of the review. In consultation with the GDG, a decision analytic model was developed to examine the cost-effectiveness of medical treatments as a first-line treatment for menorrhagia (for full results see Appendix 1). The results of the model showed that LNG-IUS generated more QALYs, at a lower cost, than any other medical treatment strategy (Table 6.1).

Table 6.1: Summary of cost-utility analysis for medical treatments at five years for a cohort of 1000 women

Treatment	Total cost (£)	Incremental cost (£)	Total effect (QALYs)	Incremental effect (QALYs)	ICER (£/QALY)
No treatment	24,000	-	2444.82	-	-
LNG-IUS	1,177,910	1,153,910	3818.89	1374.07	840
Tranexamic acid	1,490,387	312,477	3751.07	-67.82	Dominated by LNG-IUS
NSAIDs	1,529,051	351,141	3699.38	-119.50	Dominated by LNG-IUS
COCP	1,714,601	536,692	3610.71	-208.18	Dominated by LNG-IUS

6.2.3 Evidence statement on LNG-IUS

The evidence from two systematic reviews and one subsequent publication shows that LNG-IUS produces a clinically relevant reduction in MBL, in women complaining of HMB. RCTs showed this reduction to range between 71% and 95%. Evidence shows that the full benefit of treatment may not be seen for six months.

Health economics modelling conducted for this guideline shows that LNG-IUS is cost-effective when compared with both hormonal and non-hormonal treatments. It generates more QALYs at a lower cost than any other medical or surgical treatment strategy considered. When only those treatments that provide contraceptive benefits are compared, the oral contraceptive pill produces fewer QALYs at a higher cost than LNG-IUS. This analysis also considered surgery as a comparator treatment; the surgical strategy produced fewer QALYs at a higher cost than LNG-IUS.

6.2.4 GDG interpretation of evidence on LNG-IUS

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

6.2.5 Recommendations on LNG-IUS

The recommendations for LNG-IUS can be found in section 7.4.4

6.3 Combined oral contraceptives

Combined oral contraceptives (COCs) contain oestrogen and progestogen in combination. Most brands are monophasic being of the same strength throughout the 21 day treatment phase. Some vary to mimic the endogenous changes they replace. They act on the hypothalamo-pituitary axis to suppress ovulation and fertility. COCs are generally used in 21 day treatment cycles followed by a 7 day break, during which time endometrial breakdown and loss will occur. Such withdrawal bleeding is physiologically different from the bleeding that occurs after a natural ovulatory cycle. COCs have a number of general benefits and risks.²⁷³

6.3.1 Review on COC

Overview of available evidence

Two systematic reviews^{274;275} and 1 primary study²⁷⁶ were included in the review of COCs and HMB.

COC

Two systematic reviews were identified.^{274;275} The systematic reviews based their conclusions on the same RCT, which is described below.²⁷⁶

One RCT was found (n = 45) on women with menorrhagia comparing COC against naproxen, mefenamic and danazol. This comparative trial showed that COC reduced MBL by 43%, which was greater than naproxen but less than danazol or mefenamic acid. Side-effects were not reported.²⁷⁶ [EL = 1+]

Health economics studies

No health economic studies were identified on the use of COCs for HMB. Decision analytic modelling was undertaken for the guideline to assess the cost effectiveness of certain medical treatments as the first-line treatment for menorrhagia. This analysis showed that when compared with all other medical treatment strategies, the COC generated fewer QALYs at a greater cost. When compared with a strategy of 'No Treatment', the COC generated an additional 1165.89 QALYs at an additional cost of £1,690,601, for a cohort of 1000 women. The incremental cost per additional QALY is £1,450; the use of the COC pill is cost-effective when compared with a strategy of 'No Treatment'. See Appendix A for the full model results.

6.3.2 Evidence statement on COC

Evidence from one RCT of COC (ethinyl oestradiol 30ug & levonorgestrel 150ug for 21 days) on short-term outcomes, showed a reduction of MBL of 43%. The study reported no side-effects.

6.3.3 GDG interpretation of evidence on COC

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

The GDG highlighted that there is no available data on 20 ug preparations, which are also commonly used in clinical practice. The GDG also highlighted that COC has

1 other non-contraceptive benefits i.e. cycle control, less breast pain and reduced
2 dysmenorrhoea.

3

4 **6.3.4 Recommendations on COC**

5 The recommendations for COC can be found in section 7.4.4

6.4 Oral Progestogens

Progesterone is a physiological hormone produced during the luteal phase of the menstrual cycle. It is responsible for secretory transformation of the endometrium and bleeding occurs after endogenous levels of oestrogen and progesterone fall (fertilisation not having occurred). Progesterone is not available in oral formulation in the UK although vaginal preparations are available. A variety of oral synthetic progestogens are in clinical use. They vary in their potency and side-effect profiles. The mechanisms by which oral progestogens reduce menstrual blood loss are not fully understood.

6.4.1 Review on oral progestogens

Oral progestogens used in luteal phase only

Two systematic reviews were identified examining the use of progestogens during the luteal phase of the menstrual cycle.^{275;277}

The first review from 1995 (four RCTs) showed norethisterone had no effect on MBL (MBL percentage change: 95% CI = -6.1% to +1.1 %).²⁷⁵ [EL = 1+]

The second review undertaken in 2003 (seven RCTs) showed that all other pharmaceuticals tested produced greater reductions in MBL than norethisterone (vs. NSAIDs change in MBL was 22.97 ml [95% CI = -0.62 to 46.57 ml] in favour of NSAIDs; vs. danazol change in MBL was 55.63 ml [95% CI = 14.73, 96.54ml] in favour of danazol; vs. tranexamic acid change in MBL was 111.00 [95% CI = 43.54,

178.46ml] in favour of tranexamic acid; and vs. progesterone IUS change in MBL was 51.00 [95% CI = 18.38 to 83.62ml] in favour of IUS).²⁷⁷ [EL = 1++]

Detailed information from the individual RCTs included in the above reviews can be found in the evidence table.^{264;276;278-281}

One cohort study (n=16) of norethisterone and medroxyprogesterone acetate (MPA) was identified. The change in MBL associated with use of MPA was from a range of 104ml to 107.5ml prior to treatment, to a range between 72ml and 67ml after treatment. However, this study only involved five women with menorrhagia, therefore it is difficult to generalise the results.²⁸² [EL = 2-]

Oral progestogens throughout both follicular and luteal phases.

An RCT (n = 44) on women with menorrhagia examined the use of oral progestogens cyclically for 21 days compared to LNG-IUS on HMB. The trial showed an 83% reduction associated with long-term use of oral progestogens compared to a 94% reduction with LNG-IUS; the difference between groups was not statistically significant. However, 22% of women were satisfied with oral progestogens compared to 66% for LNG-IUS (no statistics provided).²⁶⁷ [EL = 1+]

Health economics studies

No health economic studies were found specifically on the use of oral progestogens for HMB.

6.4.2 Evidence statement on oral progestogens

The evidence from two reviews shows that oral progestogens taken during the luteal phase of the menstrual cycle (seven to ten days) have no effect on MBL. Evidence from one small trial shows that oral progestogen (norethisterone [15mg from day 5-26 of cycle]) used long-term, reduces MBL by 83%.

6.4.3 GDG interpretation of evidence on oral progestogens

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

The GDG discussion highlighted that:

- Other oral progestogens may be equally effective, but supportive data is not available.
- Progestogens use for heavy menstrual loss requires a long course regimen.
- Whilst use of progestogens is effective, their clinical usefulness may be limited by tolerability.

6.4.4 Recommendations on oral progestogens

The recommendations for oral progestogens can be found in section 7.4.4

6.5 Other Pharmaceuticals

Danazol is a synthetic androgenic steroid with anti-oestrogenic and antiprogestogenic activity. It is antiproliferative with respect to the endometrium and is anovulatory by inhibiting the production of gonadotrophins by the pituitary gland.

Gestrinone has actions and side-effects similar to those of danazol but is only required to be taken twice weekly as opposed to daily.

6.5.1 Review on other hormonal interventions for HMB

Overview of available evidence

Two systematic reviews^{275;283} and 1 primary study²⁸⁴ was identified.

Other hormonal interventions

One review combined the results of five RCTs examining danazol and showed a weighted average reduction in MBL of 49.7% (95% CI 47.9 to 51.6).²⁷⁵ [EL = 1+]

A second review included nine RCTs. The review found that danazol reduced MBL more than NSAIDs (1 study; WMD -96.7ml [95% CI -138.8, -54.6]) and progestogens (1 study; WMD -35.6ml [95% CI -102.2, +31]), but was also shown to cause more side-effects than NSAIDs (OR 7.0 [95% CI 1.7 to 28.2]) and progestogens (OR 4.05 [95% CI 1.6 to 10.2]).²⁸³ [EL = 1++]

Information from the individual RCTs included in the systematic reviews can be found in the evidence tables.^{264;278;279;285-287}

One small non-randomised trial (n = 37) compared gestrinone against a placebo. The study found that MBL was reduced in 15 of 19 women during the gestrinone treatment phase (p <0.01), and there was no change in MBL during placebo treatment. Side-effects included dizziness, headaches, giddiness and tiredness in both groups.²⁸⁴ [EL = 2++]

Health economics

No health economic studies were identified on the use of Danazol for HMB.

6.5.2 Evidence statement on other hormonal treatments

Research shows that danazol is effective at reducing MBL, by approximately 50%, but is associated with significant androgenic side-effects. One study shows that gestrinone, compared to placebo, reduces MBL. However, there is not enough evidence to make a recommendation about the use of Gestrinone for the treatment of HMB.

6.5.3 GDG interpretation of evidence on other hormonal treatments

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

6.5.4 Recommendations on other hormonal treatments

The recommendations for other hormonal treatments can be found in section 7.4.4

6.6 Injected/Depot Progestogens

Medroxyprogesterone acetate (Depo Provera) can be injected intramuscularly to provide contraception for the next 12 weeks. A sub-dermal etonorgestrel implant is also available. This achieves lower serum concentrations by using diffusion technology and is licensed as a contraceptive for three years. These preparations at present have no license for the treatment of HMB.

6.6.1 Review on injected progestogens for HMB

Overview of available evidence

No studies were identified on the use of injected/depot progestogens on HMB. However, there is data for the impact on MBL, specifically amenorrhea rates, when used as a contraceptive (this is taken from the NICE guideline on Long-Acting Reversible Contraceptives guideline).²⁸⁸

“Injected progestogens

In one RCT (n = 3172), significantly more Depot medroxyprogesterone acetate (DMPA) users reported amenorrhoea than norethisterone enantate (NET-EN) users (12% versus 7% and 24% versus 15% at 1 and 2 years, respectively).²⁸⁹ [EL = 1+]

One multinational RCT (n = 1216), undertaken mainly in developing countries, compared menstrual diaries in women given DMPA in 100 mg and 150 mg doses every 3 months. Amenorrhoea was experienced by 9% to 10% of women in the first three months and 41% to 47% at one year.²⁹⁰ [EL = 1-]

In a study which assessed the effect of counselling on adherence in DMPA users, amenorrhoea was the major side effect reported, occurring in 34% to 35% of the women.²⁹¹ [EL = 3]²⁸⁸

Health economics studies

No health economic studies were identified examining the use of injected progestogens for HMB.

6.6.2 Evidence statement on injected progestogens

No evidence was found relating to the use of injected progestogens for the treatment of HMB. However, evidence from the NICE guideline on Long-Acting Reversible Contraceptives highlights that amenorrhoea is a side-effect of injected progestogens. Amenorrhoea is likely to occur during use of injectable contraceptives.

6.6.3 GDG interpretation of evidence on injected progestogens

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

6.6.4 Recommendations on injected progestogens

The recommendations for injected progestogens can be found in section 7.4.4

6.7 HRT

Oestrogen replacement is used to relieve symptoms of menopause. In women with an intact uterus, progestogen opposition is added to reduce the risk of endometrial cancer that is associated with unopposed oestrogen. Hormone replacement therapy is not licensed for the treatment of HMB and may not contain a high enough dose of oestrogen or progestogen to control an irregular cycle.

6.7.1 Review on HRT for treating HMB

Overview of available evidence

No studies were identified of the use of HRT alone to treat HMB.

Health economics studies

No health economic studies of the use of HRT to manage HMB were identified.

6.7.2 Evidence statement on HRT

No evidence was identified relating to the use of HRT to treat HMB. There is insufficient evidence to make any recommendation about the use of HRT in the treatment of heavy menstrual bleeding

6.7.3 GDG interpretation of evidence on HRT

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

1 The GDG highlighted that HRT will theoretically redress the imbalance that results
2 from anovulatory cycles, but to do this an HRT with a higher dosage of progestogen
3 may be appropriate.

4

5

6.8 Gonadotrophin-releasing hormone analogue

A GnRH agonist is a synthetic peptide that acts like the natural GnRH secreted by the hypothalamus, but has a much longer biological half life. As a result, there is an initial increase in FSH and LH secretion (so-called flare effect), however after about 10 days a profound hypogonadal effect is achieved through down regulation. Generally this induced and reversible hypogonadism is the therapeutic goal. With no production of FSH or LH there is no follicular development and oestrogen production, no ovulation, no progesterone production and no menses. Thus GnRH agonists are useful in the treatment of cancers that are hormonally sensitive, i.e. prostate cancer and breast cancer. GnRH agonists are also useful in the medical treatment of oestrogen-dependent lesions such as endometriosis, adenomyosis and uterine leiomyoma. Current agonists used are given by subcutaneous or intramuscular injection or intra-nasally.

6.9 Review on GnRH-a for treating HMB

Overview of available evidence

Two primary studies were identified on GnRH-a alone. The primary aim of these studies was to examine the effect on uterine fibroids, but it did also report data on the effect in MBL.

GnRH-a

An RCT (n = 128) on women with symptomatic uterine fibroids compared leuprolide acetate depot 3.75 mg against placebo for 24 weeks. The study found that

leuprolide produced superior outcomes on menorrhagia compared to placebo (In leuprolide group (n=38): menorrhagia resolved or improved in 37, and no change or worse in 1. In the placebo group (n = 37): menorrhagia resolved or improved in 26, and no change or worse in 11). However, all reported side-effects were significantly higher in the leuprolide group compared to placebo (hot flushes: leuprolide = 52 (83%) vs. 5 (8%) placebo ($P < 0.0001$); vaginitis = 11 vs. 0 ($P < 0.0005$); arthralgia = 9 vs. 0 ($P < 0.005$); asthenia = 10 vs. 3 ($P < 0.05$); peripheral oedema = 7 vs. 1 ($P < 0.05$); insomnia = 6 vs. 0 ($p < 0.05$); nausea = 6 vs. 1 ($P < 0.05$); headaches = 18 vs. 13; depression = 7 vs. 2; emotional stability = 5 vs. 1; decreased libido = 2 vs. 0). The study concluded that treatment reduces MBL compared to placebo but with high levels of adverse effects. This shows that GnRH-a was more effective than placebo at improving subjective assessment of menorrhagia (RR = 1.39).²⁹² [EL = 1+]

An RCT (n = 67) on women with symptomatic uterine fibroids, compared depo buserelin MP 1.8m against depo leuprorelin 1.88 over 24 weeks. The study found that leuprorelin had a greater initial impact on menstrual bleeding, but by 24 weeks there was no difference between groups (Buserelin: 8-weeks = 52.9% amenorrhea; 20 weeks = 88.9% amenorrhea. Leuprolide: 8 weeks = 84.4% amenorrhea; 20 weeks = 87% amenorrhea). The difference at 8 weeks was significant ($P < 0.010$, but at 20 weeks was non-significant). The study found that leuprolide was associated with more hot flushes than buserelin (Hot flushes at 12 weeks: buserelin = 5.9% vs. 24.4% in leuprolide). The study shows that depo GnRH reduces menstrual bleeding, however, the study had high drop-out rates (11 of the Buserelin and 15 of the leuprolide group were lost to follow-up by 24 weeks).²⁹³ [EL = 1-]

6.10 GnRH-a with HRT 'add-back' therapy

Hormone replacement therapy is not licensed for the treatment of HMB and may not contain a high enough dose of oestrogen or progestogen to control an irregular cycle. It is used in combination with GnRH-a as an 'add-back' to overcome hormone related adverse effects associated with GnRH-a.

6.10.1 Review on GnRH-a with HRT 'add-back' therapy

Overview of available evidence

Results from seven RCTs examining use on GnRH-a, and 'add-back' therapy, are shown below.

GnRH with HRT 'add-back'

A crossover RCT (n = 16) on women with symptomatic uterine fibroids compared GnRH-a alone against GnRH-a with medroxyprogesterone acetate over 24 weeks. The study found that total uterine volume decreased to 73% of the baseline at 12 weeks in protocol B (mono therapy) ($p < 0.04$), but did not change in protocol A (combined therapy). After crossover at 12 weeks, the total uterine volume of women in protocol A decreased to 74% of the baseline ($p < 0.02$) at 24 weeks. A between-protocol comparison demonstrated a greater decline in total uterine volume in protocol B than A at 12 weeks, but after cross-over, MPA addition was associated with a significant increase in total uterine volume (protocol B) compared to a decrease in protocol A at 24 weeks ($p < 0.005$). The study shows that delayed use of add-back allows GnRH-a to shrink uterine fibroids. However, the study was small

and therefore results cannot be generalised. In addition, the study did not assess MBL outcomes.²⁹⁴ [EL = 1+]

An RCT (n = 16) on women with symptomatic uterine fibroids compared leuprolide only against leuprolide and medroxyprogesterone over a 24 week period. Women in group A (mono therapy) had a significant reduction in uterine size from a pre-treatment volume of 601 +/- 62 cm³ (mean +/- standard error) to a mean uterine volume of 294 +/- 46 cm³ at 24 weeks of therapy (P less than 0.01). Women in group B (combined therapy), had a reduction in uterine volume from 811 +/- 174 cm³ to 688 +/- 154 cm³, which was not statistically significant. However, only one woman in group B experienced hot flashes, whereas six women in group A had this symptom (P less than 0.01). This study suggests that simultaneous use of GnRH-a and add-back, reduces the effect of GnRH-a. However, the study was small and therefore results cannot be generalised.²⁹⁵ [EL= 1-]

An RCT (n = 51) on women with symptomatic uterine fibroids compared GnRH-a plus with either oestrogen-progestin or progestin 'add-back'. The study found that the symptoms of both groups improved (18 of 18 in the oestrogen group improved, and 14 of 17 in the progestin group improved), and that reduction in bone mineral density was similar in both groups (oestrogen-progestin: pre-treatment = 1.102, 12 weeks = 1.074, 52 weeks = 1.053.(P<0.05) Progestin: pre-treatment = 1.081, 12-weeks = 1.045, 52 weeks = 1.047.(P<0.05) Control: pre-treatment = 1.081, 52-weeks = 1.078 (NS)). The study concluded that the regimen were equivalent and could be used as a long-term alternative to surgery for women with uterine fibroids. However, the high drop-out rate (16 of 51) was of concern.²⁹⁶ [EL = 1-]

1
 2 An RCT (n = 12) on women with symptomatic uterine fibroids, compared GnRH-a
 3 against GnRH-a with estriol 'add-back' over 6 months. The study found a reduction
 4 in mean fibroid size of 53.6% by 2 months and a further 31.3% by 6 months in the
 5 non-add back group, and in the 'add-back' group, a reduction in mean fibroid size of
 6 59.1% by 2 months and a marginal further reduction by 6 months. Bone mineral
 7 density reduced to 96.5% of it's original density by 2 months, and 92.5% by 6
 8 months in the non-add back group, but bone mineral density did not change
 9 significantly in the 'add-back' group. The study concluded that GnRH-a plus estriol
 10 add-back therapy might be considered for long-term treatment of uterine
 11 leiomyomata. However, the study was small and therefore results cannot be
 12 generalised.²⁹⁷ [EL = 1-]

13
 14 An RCT (n = 50) on women with symptomatic uterine fibroids compared GnRH-a
 15 plus placebo against GnRH-a plus tibolone, over a 6-month period. The study found
 16 that menorrhagia improved in both groups (average menorrhagia scores (0 to 10):
 17 Baseline = 8.2 vs. 8.0, 6-months = 0 vs. 2.5 (both $p < 0.01$ from baseline)), but bone
 18 mineral density (g/cm³) was reduced least in the tibolone group (baseline: 1.056 vs.
 19 1.044, 6-months: 1.002 vs. 1.035, $P < 0.01$ for placebo group vs. baseline and vs.
 20 treatment). The study concluded that administration of tibolone in association with
 21 GnRH-a reduces vasomotor symptoms and prevents bone loss, without
 22 compromising the therapeutic efficacy of GnRH-a alone.²⁹⁸ [EL = 1-]

23
 24 An RCT (n = 100) on women with symptomatic uterine fibroids compared GnRH-a
 25 plus raloxifene against GnRH-a plus placebo. The study found that BMD levels fell

significantly in the placebo group in comparison to the baseline and treatment group ($p < 0.05$). The study concluded raloxifene prevents GnRH-a related bone loss in pre-menopausal women with uterine leiomyomas. The study did not assess MBL outcomes.²⁹⁹ [EI = 1-]

Further results from this RCT examined the QoL impact of treatment against placebo and against healthy controls (GnRH-a plus raloxifene ($n = 45$) vs. GnRH-a plus placebo ($n = 46$) vs. normal population ($n = 50$). The study found that cognitive functioning was adversely affected by treatment, but that QoL was improved (Kupperman index (0 to 51), Baseline = 2.6 (1.2) vs. 2.1 (1.1) vs. 2.1 (1.2); 6th cycle = 22.8 (3.9) vs. 25.6 (4.2) vs. 2.5 (1.3); SF-36 Baseline = 50.4 (14.1) vs. 52.6 (14.5) vs. 84.2 (10.4); 6th cycle = 80.3 (11.5) vs. 81.7 (12.6) vs. 83.4 (10.2))). The paper concluded that GnRH-a causes a reduction in cognitive functioning in women with symptomatic fibroids, but improves QoL to near normal levels.³⁰⁰

An RCT ($n = 12$) on women with symptomatic uterine fibroids compared GnRH-a against placebo over 24 weeks. The study found that uterine volume and myoma volumes were improved in the treatment group, but worsened in the placebo group (placebo versus treatment: Uterine volume at baseline = 457 cm³ vs. 645 cm³ (ns); post-treatment uterine volume = 656 cm³ vs. 467 cm³ ($P < .02$); Myoma volume: baseline = 267 cm³ vs. 402 cm³, post-treatment 417 cm³ vs. 334 cm³ ($P = .06$)). The study concluded that temporary hypoestrogenism induced by GnRH analogues can produce a significant, though temporary, reduction in uterine volumes, and that the non-myoma volume is responsible for much of the reduction

and enlargement. However, the study was small and therefore results cannot be generalised.³⁰¹ [EL = 1-]

Health economics studies

No health economic studies on the use of GnRH-s and HRT 'add-back' to manage HMB were identified.

6.10.2 Evidence statement on GnRH-a

Evidence from 2 trials shows that GnRH-a reduces MBL, in the form of amenorrhea, with a RR (relative risk) of 1.39 for improvement in MBL, and amenorrhea rates of 89%. However, GnRH-a is associated with significant side-effects, including perimenopausal symptoms, headaches and nausea.

Evidence from seven RCTs show that GnRH-a, plus add-back therapy, is an effective treatment for uterine fibroids. However, there is only limited evidence on the effect on HMB, and the long-term (beyond 6-months) adverse effects of this treatment have yet to be shown.

6.10.3 GDG interpretation of evidence on GnRH-a

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

6.10.4 Recommendations on GnRH-a

The recommendations for GnRH-a can be found in section 7.4.4

7 Non-hormonal medical treatments for HMB

Endometrial proliferation, secretory transformation and withdrawal bleeding are regulated by the hormonal cycle but the precise biochemical mechanisms are still not fully understood. Where HMB is a problem but hormonal therapy is declined or inappropriate non hormonal pharmaceuticals may be able to offer benefit through their effect on the physiology of menstrual loss. These are not contraceptive and can be used in women seeking to become pregnant as they are initiated each cycle at the onset of bleeding.

Figure 7.1 shows a schematic of all the RCT comparisons that have been undertaken for pharmaceutical treatments. What this figure highlights is the variable amount of RCT evidence available comparing each treatment.

7.2 Tranexamic acid

Tranexamic acid inhibits factors associated with blood clotting but has no effect on coagulation within healthy blood vessels. There is no increase in the overall rate of thrombosis within those taking tranexamic acid compared to those not taking the drug when large communities are studied.

Tranexamic acid is a competitive inhibitor of plasminogen activation. It does not appear to affect platelet numbers or aggregation but acts to reduce the breakdown of fibrin in a preformed clot. As menstrual bleeding involves liquefaction of clotted

blood from spiral endometrial arterioles, reduction in this process is believed to be the mechanism of reduced menstrual loss. Dosage for menorrhagia is 1g (2x 500mg tablets) 3 to 4 times daily, from the onset of bleeding for up to four days.

7.2.1 Review on Tranexamic Acid for treating HMB

Overview of available evidence

This review includes 3 systematic reviews. No additional or subsequent primary studies were identified relating to those studies included in the systematic reviews.

Tranexamic Acid

The three reviews reported a range of MBL reduction depending on the studies included, but there was agreement that tranexamic acid produced a clinically important reduction in MBL in women with HMB.^{275;302;303} The main difference was between the inclusion and exclusion of studies involving women with or without IUD induced menorrhagia.

The first review pooled results from 7 trials and found a percentage reduction in MBL of 46.7 (95% CI 47.9-51.6) with tranexamic acid.²⁷⁵ [EL = 1+]

The second review undertook a meta-analysis of two RCTs of tranexamic versus placebo and found a difference of -93.96ml (95% CI -151.43 to -36.49), p=0.001, in favour of treatment.³⁰² [EL = 1++]

A third review based on five trials concluded that oral tranexamic acid 2.0 to 4.5g daily for 4 to 7 days per cycle reduced menstrual blood loss by between 34% to 59%

over 2-3 cycles, and that 12% of women reported adverse events, such as nausea, vomiting, diarrhoea and dyspepsia. There were no reports of deep vein thrombosis (DVT) in any study in any of the reviews.³⁰³ [EL = 1+]

Additional data from individual RCTs is available in the evidence table.^{281;304-309}

Health economics studies

No health economic studies were identified on the use of tranexamic acid to treat HMB. Decision analytic modelling was undertaken for the guideline to assess the cost effectiveness of certain medical treatments as the first-line treatment for menorrhagia. This analysis showed that tranexamic acid generated fewer QALYs (3751.07) at a greater cost (£1,490,387) than the LNG-IUS (3818.89; £1,117,910). When compared with other non-hormonal treatments (NSAIDs), tranexamic acid generated more QALYs at a lower cost; NSAIDs generated 3699.38 QALYs at a cost of £1,529,051. When compared with a strategy of No Treatment, tranexamic acid generated an additional 1306.25 QALYs at an additional cost of £1,466,387, giving an incremental cost per QALY of £1,122. Tranexamic acid is cost-effective when compared with either NSAIDs or No Treatment, but not when compared with LNG-IUS. See Appendix A for the full model results.

7.2.2 Evidence statement on tranexamic acid

There is sufficient evidence based on RCT studies to make a recommendation on the use of tranexamic acid, but no evidence for other antifibrinolytics. Tranexamic acid at a dose of 2.0 to 4.5g per day for 3-5 days from the onset of bleeding causes a clinically significant reduction in MBL for women with HMB, ranging from 29% to

58% in studies lasting up to a year. However, there are no long-term follow-up studies.

The results from the economic modelling show that when hormonal treatment methods are not considered acceptable, tranexamic acid generates more QALYs at a lower cost than NSAIDs, and more QALYs but at a greater cost than a strategy of no treatment. The cost per additional quality adjusted life year when comparing tranexamic acid with No Treatment is £1,122.

7.2.3 GDG Interpretation of evidence on tranexamic acid

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

The GDG also highlighted that tranexamic acid:

- does not reduce dysmenorrhoea/pain associated with bleeding, so advice on suitable pain relief is needed may be required
- is not a contraceptive, so advice on suitable contraceptives is recommended, if required.
- does not regulate cycles, so advice and suitable additional treatment should be given, if required.

7.2.4 Recommendations on tranexamic acid

The recommendations for tranexamic acid can be found in section 7.4.4

7.3 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

A variety of NSAIDs have been used to treat HMB. These agents reduce prostaglandin synthesis by inhibition of cyclo-oxygenase. Prostaglandins affect local tissue reactivity and are implicated in inflammatory response, pain pathways, uterine bleeding and uterine cramps. HMB can be associated with increased prostaglandin levels. NSAIDs should be taken from the onset of bleeding, or just before, until heavy loss has abated.

7.3.1 Review on NSAIDs for treating HMB

Overview of available evidence

Two systematic reviews met the inclusion/exclusion criteria. No additional or subsequent primary studies were identified relating to those studies included in the systematic reviews.

NSAIDs

One systematic review undertook meta-analysis on individual NSAIDs and found a range of responses. The highest being for mefenamic acid and lowest ibuprofen (mefenamic acid (pooled results for 10 studies): reduction in MBL = -29% [95% CI 27.9 to 30.2]. diclofenac (2 studies) reduction in MBL = -26.9% [23.3 to 30.6]. Naproxen (5 studies): reduction in MBL = - 26.4% [24.6 to 28.3]. Ibuprofen (3 studies) reduction in MBL = -16.2% [13.6 to 18.7]).²⁷⁵ [EL = 1++]

A second review included only 1 placebo-controlled study, but several comparative studies. The analysis showed that NSAIDs reduced MBL, but that tranexamic acid

and danazol produced greater reductions (NSAIDs vs. placebo (1 study [n = 11]): difference in reduction of MBL = -124ml [95% CI -186.36 to -61.64]. NSAIDs versus tranexamic acid (1 study [n = 48]): difference in reduction of MBL = +73 [21.66 to 124]. NSAIDs vs. etamsylate (2 studies [n=82]): difference in reduction of MBL = -42.88 [-86.25 to 0.50]. NSAIDs vs. danazol (3 studies [n=79]): difference in reduction of MBL = 45.06 [18.73 to 71.39]. NSAIDs vs. oral progestogens (2 studies [n=48]): difference in reduction of MBL = -22.97 [-46.57 to 0.62]. NSAIDs vs. IUD (1 study [n=16]) difference in reduction of MBL = -4 [-31.23 to 23.23]. NSAID vs. oral contraceptive (1 study [n = 26]) difference in reduction of MBL = 25.25 [-22.34 to 72.84]). However, NSAIDs had a better side-effect profile than danazol, and a similar one to Tranexamic acid.³¹⁰ [EL = 1++]

Further information on individual RCTs can be found in the evidence table
264;276;286;307;308;311-320

Health economics studies

No health economic studies were identified on the use of NSAIDs to treat HMB. Decision analytic modelling was undertaken for the guideline to assess the cost effectiveness of certain medical treatments, as the first-line treatment for menorrhagia. This analysis showed that NSAIDs generated fewer QALYs (3699.38) at a greater cost (£1,529,051) than either the LNG-IUS (3818.89; £1,117,910) or tranexamic acid (3751.07; £1,490,387). The LNG-IUS and tranexamic acid are cost-effective alternatives when compared with NSAIDs. When compared with a strategy of No Treatment, NSAIDs generated an additional 1254.56 QALYs at an additional cost of £1,505,051 giving an incremental cost per QALY of £1,199. NSAIDs are

cost-effective when compared with a strategy of No Treatment. See Appendix A for the full model results.

7.3.2 Evidence statement on NSAIDs

Overall, the evidence suggests that NSAIDs (mefenamic acid or naproxen) produce a clinically important reduction in MBL. Reported reductions in MBL ranged from 20% to 49%. NSAIDs were not as effective as danazol or tranexamic acid, but had a better safety profile than the danazol. The systematic reviews on which this statement is based are themselves based on an RCT. NSAIDs were found to be cost-effective when compared with No Treatment, but generated fewer QALYs at a greater cost than LNG-IUS or tranexamic acid.

7.3.3 GDG Interpretation of evidence on NSAIDs

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

In addition, the GDG highlighted that:

- NSAIDs are not contraceptives, so advice on suitable contraceptives is recommended, if required.
- NSAIDs are additionally beneficial for the treatment of dysmenorrhoea.
- NSAIDs should not be used where it is thought that HMB is caused by bleeding disorders.
- Due to the cyclical nature of use, well known side-effects associated with long-term use of NSAIDs are reduced.

- 1 ▪ There is no evidence regarding the effect of NSAIDs on HMB in the presence
- 2 of uterine fibroids.
- 3 ▪ NSAIDs should not be used where it is thought that HMB is caused by
- 4 coagulation bleeding disorders.

6 **7.3.4 Recommendations on NSAIDs**

7 The recommendations for NSAIDs can be found in section 7.4.4

9 **7.4 Etamsylate**

10 Etamsylate is believed to reduce bleeding from capillaries by correcting anomalies of

11 platelet adhesion. It does not appear to affect the fibrin cascade. It is taken as

12 500mg four times daily from, but not before, the onset of bleeding.

14 **7.4.1 Review on etamsylate for treatment HMB**

15 *Overview of available evidence*

16 Three systematic reviews were identified that assessed the use of etamsylate.

17 ^{275;302;310} No additional or subsequent primary studies were identified with regard to

18 those studies included in the systematic reviews.

20 One review pooled results of four studies and found etamsylate reduced MBL in

21 HMB by 13.1% (95% CI 10.9 to 15.3), but this was less than most other

22 interventions. ²⁷⁵ [EL = 1+]

A review compared etamsylate against NSAIDs, and found NSAIDs were more effective at reducing MBL (reduction in MBL for NSAIDs vs. etamsylate = -42.88 ml/cycle [95% CI: -86.25 to 0.50]). (21384) [EL = 1++]

A review compared antifibrinolytics against etamsylate, and found the former reduced MBL more than the latter (antifibrinolytics vs. etamsylate (1 study): reduction in MBL = -97ml [-134.36 to -59.64] in favour of tranexamic acid).³⁰² [EL = 1++]

Information on individual RCTs included in the reviews can be found in the evidence table.^{307;312;321}

Health economics studies

No health economic studies were identified on the use of etamsylate for the treatment of HMB.

7.4.2 Evidence statement on Etamsylate

The evidence on the MBL change for etamsylate is insufficient, with figures from one review reporting that etamsylate reduces MBL by an average of 13.1%, but that this is less than other pharmaceutical treatments.

7.4.3 GDG Interpretation of evidence on etamsylate

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects.

7.4.4 Recommendations on pharmaceutical treatments for women with HMB

When pharmaceutical treatment is felt to be necessary and hormonal treatment is acceptable to a woman with HMB, then the order in which interventions should be considered is:

- First line, LNG-IUS^{xiii} [A]
- Second line, tranexamic acid [A] or NSAIDs [A] or COCs^{xiv} [B]
- Other treatment options for consideration are: Norethisterone (15mg) daily from days 5 to 26 of the cycle or Injected long acting progestogens.^{xv} [A]

^{xiii} World Health Organisation Medical Eligibility Criteria for Contraceptive Use (WHOMEC) criteria apply. These involve the assessment of the individuals' suitability for contraceptives, based on their specific profile of potential benefits and harms. This allows informed decision-making by the woman prior to the start of treatment.³²²

^{xiv} World Health Organisation Medical Eligibility Criteria for Contraceptive Use (WHOMEC) criteria apply. These involve the assessment of the individuals' suitability for contraceptives, based on their specific profile of potential benefits and harms. This allows informed decision-making by the woman prior to the start of treatment.³²³

^{xv} Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of injected progestogen is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

When pharmaceutical treatment is felt to be necessary and hormonal treatment is not acceptable (for example, if a woman is wishing to conceive) to women with HMB then the order in which treatments should be considered is:

First line, tranexamic acid,

Second line, NSAIDs. **[A]**

Use of NSAIDs or Tranexamic acid should be stopped if they do not improve symptoms within 3 months. **[D(GPP)]**

Ongoing use of NSAIDs and tranexamic acid can be recommended for as long as they are found to be beneficial by women with HMB. **[D(GPP)]**

When HMB coexists with dysmenorrhoea then NSAIDs should be preferred to tranexamic acid. **[D(GPP)]**

A second medical treatment should be considered when a first-line medical treatment has failed for women with HMB. **[D]**

Women should be fully counselled regarding the changes to the bleeding pattern particularly in the first few months post-insertion of an LNG-IUS. Perseverance for at least 6-months is recommended for benefits to be appreciated **[D (GPP)]**

Oral progestogens given during the luteal phase only should not be used to treat women with HMB. **[A]**

1

2 Danazol is not recommended for routine use in the treatment of HMB. **[A]**

3

4 GnRH-a could be considered when all other management options, including surgery
5 or UAE, are contraindicated for the treatment of a woman. If it is to be used for more
6 than 6 months then 'Add-Back' therapy is recommended ^{xvi} **[B]**

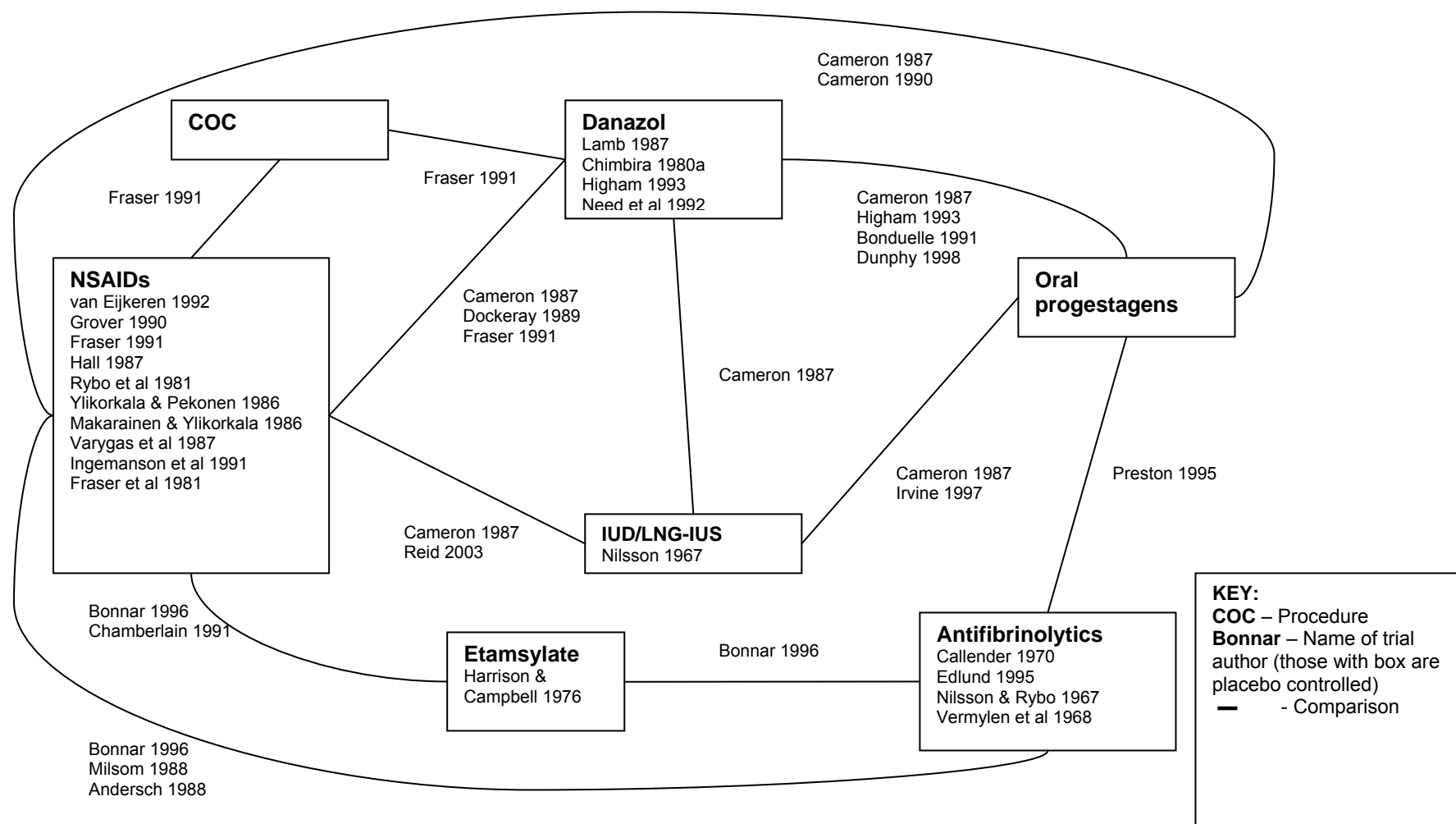
7

8 Etamsylate should not be used in the treatment of HMB. **[A]**

^{xvi} Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of GnRH-a is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

1 **Figure 7.1 - Schematic of RCT evidence for pharmaceutical interventions for HMB**^{264;267;271;276;278-280;286;287;304;304-308;308;309;311;312;314-}

2 316;318-321;324-328



3

1

2 **NOTE: A table will appear here summarising the outcome data for each pharmaceutical intervention.**

8 Indications for non-hysterectomy surgery or interventional radiology

Clinical indications for surgery or interventional radiology are defined as those symptoms where the impact of symptoms cannot be treated by any other means, or would benefit from a referral to a more specialist clinician. Women's preferences are the opinions and beliefs of a woman with regard to the outcome that they want from treatment, and what level of type of treatment they are willing to accept in order to achieve that outcome. Initially referral for non-hysterectomy procedures are assessed as these are different from those used to indicate hysterectomy.

8.2.1 Review on indications for surgery (not hysterectomy) or interventional radiology

Overview of available evidence

No RCTs or systematic reviews of RCTs were identified. Therefore, reviews of observational studies were included. In total, three primary studies are included.

Indications for surgery (not hysterectomy) or interventional radiology

A prognostic study (n = 130) on women who had undergone thermal balloon endometrial ablation, showed that only endometrial thickness and the position of uterus impacted on the success of the outcome. Therefore, these factors should be taken into account prior to undertaking balloon ablation.³²⁹. [EL = 3]

A patient preference study (n = 96) assessing women's reason for choosing treatment for HMB, found that the majority of women were willing to accept a 50:50 chance of treatment failure in order to avoid hysterectomy.²⁴⁷ [EL = 3]

A third patient preference study (n = 221) examined women's priorities for treatment of menorrhagia. The study that 'stops periods for good' and 'back to usual activities as soon as possible' were the two most importance wishes of women.²⁴⁸ [EL = 3]

8.2.2 Evidence statement on indications for surgery (not hysterectomy) or interventional radiology

Evidence from three observational studies provided limited evidence on the indications for surgery. What these studies highlight is that a combination of physical criteria and a woman's preference will determine appropriateness of surgery.

8.2.3 GDG Interpretation of evidence on indications for surgery (not hysterectomy) or interventional radiology

Given the lack of high quality evidence on indications for surgery, the GDG relied upon the experience of the group in order to make recommendations.

8.2.4 Recommendations on indications for surgery (not hysterectomy) or interventional radiology

Surgery (excluding hysterectomy) should be considered in cases of HMB where bleeding is: having a severe impact on a woman's quality of life, and the woman has completed her family (except in the case of UAE or myomectomy where fertility is potentially retained). [C]

1

2 Women should be made aware of the impact on fertility that surgery will have in all
3 cases. **[D(GPP)]**

4

5 Endometrial ablation should be considered in women who have a normal uterus and
6 small uterine fibroids (< 3cm). **[A]**

7

8 For women with large fibroids in presence of HMB, and other significant symptoms
9 (dysmenorrhoea; pressure symptoms), referral for consideration of surgery or UAE
10 as a first line can be recommended. **[D(GPP)]**

9 Surgery as first line treatment for HMB

Women with HMB can choose from pharmaceutical or operative interventions. However, it is unclear if operative interventions should be used as the initial treatment for HMB or if a pharmaceutical intervention should always be first tried. The answer to this question depends on a number of issues, but one is the degree to which pharmaceutical or operative techniques control HMB.

9.2.1 Review on surgery as first line treatment for HMB

Overview of evidence

One systematic review and one subsequent RCT were identified.

Surgery as first line treatment

One systematic review undertaken in 2006 that included eight RCTs (n = 821) compared pharmaceutical with surgical treatments for HMB. Two RCTs included in the systematic review examined use of pharmaceutical or surgical interventions on women with HMB in a secondary care setting. The study showed that the difference between pharmaceutical treatments (LNG-IUS was not available at this time) and surgery diminished over time until by five-years follow-up, there was no statistical difference between the groups. In relation to control of bleeding (cure or improvement) the figures were: at 4-months (n = 186) OR was 10.62 (5.3 to 21.27) in favour of surgery; and by 2-years (n = 173) OR was 2.39 (1.21 to 4.70) in favour of surgery, and by 5-years (n = 140) OR was 1.99 (0.84 to 4.73) with no statistical difference between the groups. The figures for patient satisfaction were: at four-

months (n = 183) OR = 8.28 (4.29 to 15.97) in favour of surgery; by two-years (n = 173) OR = 2.83 (1.46 to 5.50) in favour of surgery; and by five-years (n = 140) OR was 1.69 (0.77 to 3.70) with no statistical difference between the groups. However, women in the pharmaceutical group were more likely to undergo additional surgery: by two-years follow-up (n = 236) OR was 0.12 [0.06, 0.22] in favour of surgery and by five-years follow-up (n = 140) OR was 0.11 (0.06 to 0.22) in favour of surgery. Given that the study used intention-to-treat, this is likely to mean that a high proportion of women in the medical group had had surgery, and this is likely to cause an attenuation of effect-size.³³⁰ [EL = 1++]

Six other RCTs were included in the review that compared LNG-IUS with surgery (hysterectomy, ablation) in secondary care settings, and concluded that the treatments were equivalent. The figures showed that objective measurement of MBL at 12 months was in favour of surgery (1 RCT, n=223, OR 25.72 [1.5, 439.98]). Also, the subjective measurement of MBL at 12 months was in favour of surgery (3 RCTs, n=189, OR = 3.99 [95% CI 1.53, 10.38]). However, results from QoL measures were more mixed, with no difference being found between groups on the SF-36 scale for general health, physical function, mental health, vitality and physical role limitation. Statistically significant differences were found between the groups, on the SF-36 scale, for emotional role (n = 269, WMD = 9.67 [1.65 to 17.69]), social function (n = 274, WMD = 3.64 95% CI [-1.14 to 8.43]), and bodily pain (n = 274, WMD = 6.98 [95% CI 1.68 to 12.29]) in favour of surgery. In addition, women using LNG-IUS were more likely to undergo additional surgery at 12 months ((n = 423) OR 0.11 (95% CI 0.04 to 0.30)) and were less likely to have reported adverse effects (OR 0.24 [95% CI 0.11, 0.49]).³³⁰ [EL = 1++]

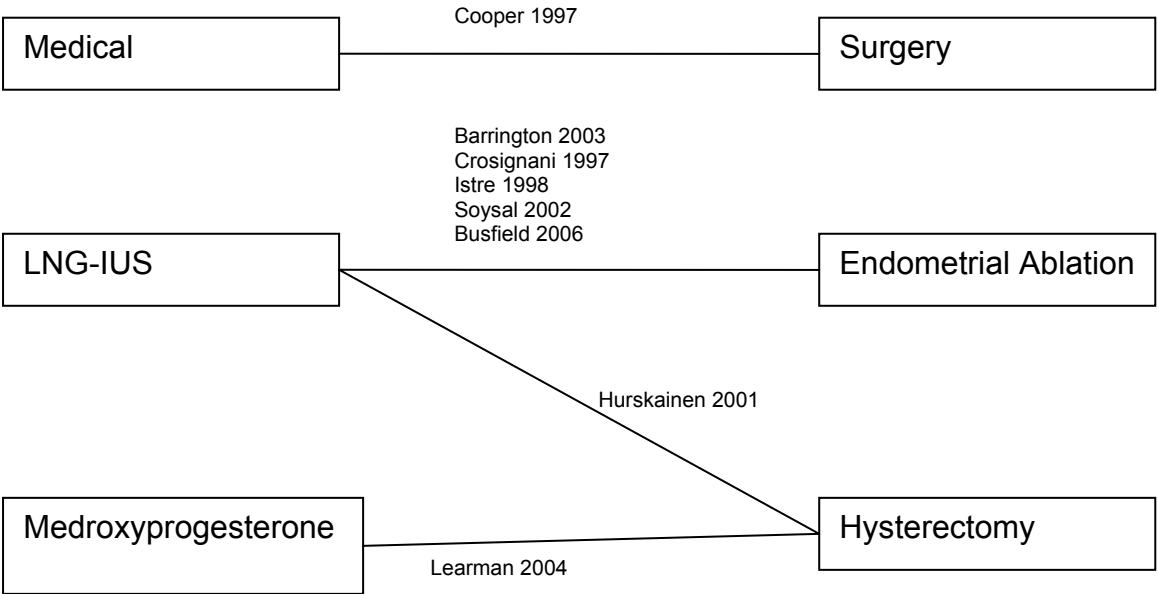
1

2 The review concluded that, "Surgery reduces menstrual bleeding at one year more
3 than medical treatments, but LNG-IUS appears equally beneficial in improving
4 quality of life and may control bleeding as effectively as conservative surgery over
5 the long term. Oral medication suits a minority of women long term". ³³⁰ [EL = 1++]

6

7 Further information on individual RCTs is available in the evidence table
8 121;246;262;265;266;268;270;272;331

1 **Figure 9.1** - Schematic of RCT evidence on medical versus surgical interventions



2

3 106;120;121;262;265;272;332;333

4

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6

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9.2.2 Evidence statement on surgery as first treatment for HMB in secondary care

One systematic review was available. The review shows that, in secondary care settings, surgery has a slight advantage over pharmaceutical treatments, and that this diminishes with time (control of bleeding at 5-years (n = 140) OR = 1.99 (0.84 to 4.73)) in favour of surgery). However, this result may be due to nearly 90% of the pharmaceutical group undergoing surgery over the follow-up period. In one RCT included in the review (where Mirena was not available), results showed that women who underwent immediate surgery had statistically higher QoL at five-years than those who underwent surgery after failed pharmaceutical treatment. The review did not examine how the presence of fibroids influenced outcomes. Whilst surgery has an advantage over pharmaceutical treatment in terms of outcome, this does not take into account the reversible nature of pharmaceutical treatment compared to surgery.

9.2.3 GDG Interpretation of evidence on surgery as the first treatment for HMB in secondary care

In their interpretation of the evidence, the GDG placed a high value on women avoiding hysterectomy and retaining their uterus. Furthermore, the GDG assumed a lower effect of pharmaceutical treatment in the presence of uterine fibroids, as shown in pharmaceutical studies.

The GDG recognised the effectiveness of LNG-IUS at controlling MBL, as shown by RCT evidence. However, the GDG discussion focused on the high level of subsequent surgery associated with pharmaceutical interventions, and data

1 suggesting that women who delay having surgery in order to try pharmaceutical
2 treatment (in a secondary care setting) and subsequently have surgery, have worse
3 long-term QoL than women who have immediate surgery. However, it was noted
4 that this interpretation was based on data obtained prior to LNG-IUS being available.

5
6 **9.2.4 Recommendations on surgery as the first treatment for HMB in**
7 **secondary care**

8
9 Endometrial ablation may be offered to women with HMB as an initial treatment in
10 secondary care after full discussion of outcomes and other treatment options. **[A]**

11
12 Hysterectomy should not be used as a first line treatment solely for HMB, unless in
13 the presence of large fibroids, or other symptoms. **[D(GPP)]**

10 Non-hysterectomy surgery for HMB

10.2 Dilation and Curettage

Dilation & Curettage is mainly used in HMB as a diagnostic tool, as it allows for testing of the endometrial material collected.

10.2.1 Review of dilation and curettage

Overview of available evidence

Only one observational study was identified and there were no systematic reviews or RCTs.

Dilation and curettage

The observational study (n = 22) graphically (no figures provided) showed that menstrual blood loss was reduced for one month after D&C, but then returned to previous levels.³³⁴ [EL = 2-]

10.2.2 Evidence statement of dilation and curettage

Limited evidence is available on the use of therapeutic D&C for HMB, but the one study that was identified showed that any effect was temporary.

10.2.3 GDG Interpretation of evidence of dilation and curettage

Given the limited evidence, the GDG recommendation was based upon clinical experience.

10.2.4 Recommendations on dilation & curettage

D&C should not be used as a therapeutic treatment for HMB. [C]

10.3 Endometrial ablation / resection

Prior to the widespread introduction of endometrial ablation methods early in the 1990s, a hysterectomy was the only definitive method available if medical treatment did not work or was not suitable. Since then, a number of surgical alternatives have become available. These methods all aim to destroy or remove the endometrium along with the superficial myometrium (uterine muscle). By doing this, the expectation is that most or all of the glands from which the endometrium develops will be destroyed, greatly reducing or stopping completely menstrual blood loss.

The first procedures to be developed (first generation) involved distending the uterine cavity with fluid and either resecting the tissue with a electrosurgical loop, Transcervical Resection of the Endometrium (TCRE), ablating it with an electrosurgical ball, Rollerball Ablation, or using a laser, Endometrial laser ablation (ELA). All these methods are performed under vision and are skill dependent. They all have a risk of absorption of the fluid used to distend the uterus into the blood stream.

As these methods are relatively difficult to learn, new methods were developed to avoid this. These second generation methods are in general not performed under direct vision, and are easier to learn and hopefully safer to use. This group include Thermal Balloon Ablation (TBA), Microwave Endometrial Ablation (MEA), Hydrothermablation (HTA) and Endometrial Cryotherapy.

All these procedures involve minor surgery that is usually possible as day cases and some with local anaesthetic. The endometrial ablation methods all vary in their applicability but in general are used to treat HMB for women who have a uterus that is not greatly enlarged and does not contain large fibroids, distorting the uterine cavity.

10.3.1 Review of endometrial ablation/resection

Overview of available evidence

Three systematic reviews of RCTs were identified. No subsequent or additional RCTs were identified. A number of observational studies were identified but have not been included in the review due to the availability of good RCT evidence.

EA versus other treatments

A systematic review in 1999 (five RCTs) compared hysterectomy and endometrial ablation. The review found that, in terms of reduction in MBL, hysterectomy provided greater reductions (at 12 months [3 studies, n = 440] OR was 0.12 [0.06 to 0.25]). Patient satisfaction also favoured hysterectomy (At 12 months [3 studies, n = 519] OR was 0.46 [0.24 to 0.88] and at 24 months [3 studies, n = 354] OR was 0.31 [0.16 to 0.59]). Quality of life measures (SF-36) showed no difference between groups, except for general health (p = 0.02), pain (p = 0.007), and social functioning (p = 0.007), that were all in favour of hysterectomy. However, endometrial ablation techniques required less time to undertake ((5 studies, n = 706, WMD = -23.06 [95% CI -23.80 to -22.32]) in favour of ablation/resection), shorter hospital stays (5 studies, n = 706, WMD = -4.91 [95% CI -4.95, -4.87]) and fewer adverse events Of the 13

types of adverse events reported, results favoured ablation/resection over hysterectomy for eight of these, and five were no different. However, more women in the endometrial ablation groups required further surgery within 12-months (five studies, n = 706, OR was 7.33 [4.18 to 12.86]). The study concludes that ablation/resection is an alternative to hysterectomy, but is less effective at reducing MBL and improving satisfaction. However, ablation/resection does lead to better QoL, shorter surgery and fewer complications.³³⁵ [EL= 1++]

A number of RCTs were also identified comparing ablation against LNG-IUS and other medical treatments. These are reviewed in the chapter 9.^{262;265;268;270;272;336-338}

Endometrial ablation/resection

A systematic review undertaken as part of a HTA report (two reviews and ten RCTs, search date 2002) examined the effectiveness and safety of MEA and TBEA for HMB. The study found amenorrhoea rates at 12-months reported by seven trials ranged from 36% to 40% for MEA and from 10% to 40% for TBEA. The review also reported significant reductions in levels of MBL or reclassification of bleeding patterns for both MEA and TBEA. The review found high levels of satisfaction (>75%) for both MEA and TBEA. The study concluded that both MEA and TBEA were equivalent to first-generation ablation techniques.³³⁹ [EL = 1+]

A second systematic review (19 RCTs, search date 2005) compared the various ablation techniques against one another for treatment of HMB. Only limited differences were found when comparing one ablation method against another.

Below the comparison undertaken in this review is outlined, but only the statistical significant differences between treatments are reported.³⁴⁰ [EL = 1++]

Laser ablation versus TCRE

Two RCTs (n = 388) were identified. Laser ablation took longer (9 minutes (WMD: 9.15)) and equipment was more likely to fail (OR = 6 [CI 1.7 to 20.9]. There was no difference between methods for amenorrhoea rates, satisfaction, QoL or complications.

Vaporising electrode versus TCRE

One RCT (n = 91) was identified. TCRE was more likely to be difficult to perform (OR = 0.25 [CI 0.09 to 0.73]), and had greater fluid deficit (WMD = 258 ml [CI 173.9 to 342.1]) and took longer to perform (WMD = +1.5 minutes [CI 0.35 to 2.65]). No difference between methods for amenorrhoea rates, satisfaction or QoL. However, it is unclear how similar vaporising ablation is to REA; and if the two should be differentiated.

REA versus TCRE

There was no difference between techniques on future hysterectomy or re-surgery at two and five years follow-up.

Thermal laser versus TCRE

One RCT (n = 111) was identified. Amenorrhoea rates were higher at one and three years follow-up in the thermal laser group (OR = 4.9 [95% CI 2.2 to 11.0] at 1-year, OR = 4.6 [95% CI 2.04 to 10.5] at 3-years). The mean length of surgery was shorter

in the thermal group (WMD = 9.3 [CI 11.4 to 7.2]). There were no differences between groups for menorrhagia, re-surgery, complications or satisfaction.

Hydro thermoblator versus REA

One RCT (n = 269) was identified. Hydro patients were more likely to have local than general anaesthesia (OR = 2.85 [CI = 1.6 to 5.1]). Hydro patients were less likely to experience hematometra (OR = 0.18 [CI 0.03 to 0.93]), but more likely to have abdominal pain (OR = 1.85 [CI 1.1 to 3.1]) and nausea (OR = 3.7 [CI 1.5 to 9.0]).

Cryoablation versus REA

Two RCTs (n = 279) were identified. The cryoablation group were less likely to have amenorrhoea at one year (OR = 0.3 [CI 0.2 to 0.6]), but more likely to have local than general anaesthesia (OR 13.2 [CI 5.8 to 30.0]). There were no differences in satisfaction rates, success rates (PBAC <75), menorrhagia rates or hysterectomy rates.

Electrode ablation (balloon or mesh) versus TCRE

Two RCTs (n = 520) were identified. The operative time with TCRE was longer (WMD = 18.7 minutes [CI 16.8 to 20.7]). The electrode group were more likely to have local than general anaesthesia (OR = 15.9 [CI 10.1 to 25.1], and less likely to have cervical tears or lacerations (OR = 0.11 [CI - 0.01 to 0.9]). There was no difference between groups in amenorrhoea rates, complications rates, 12-month PBAC, satisfaction rates or need for hysterectomy.

1 *MEA versus TCRE plus rollerball*

2 One RCT (n = 322) was identified. At two-years follow-up, microwave was more
 3 satisfactory and acceptable than TCRE (OR = 1.9 [CI 1.1 to 3.3], OR = 2.7 [1.1 to
 4 6.8]). At five-years follow-up, the difference was maintained (OR = 2.3 [CI 1.22 to
 5 4.3], OR = 3.7 [CI 1.3 to 10.1]). The hysterectomy rate following MEA was
 6 significantly lower (18% versus 28%). In addition, odds of haemorrhage were lower
 7 in the microwave group (OR = 0.14 [CI 0.02 to 0.8]). However, equipment failure
 8 rates (OR 4.07 [CI 1.1 to 15]), vomiting (OR = 4 [CI 1.4 to 11.7]), and uterine
 9 cramping (OR = 1.7 [1.1 to 2.8]) were greater in the MEA group. There were no
 10 differences in other outcomes or in the same outcomes at different time periods.

11

12 *TBEA versus REA*

13 One RCT (n = 239) was identified. Amenorrhoea was less likely with TBEA at 12
 14 and 36 months (OR 0.6 [CI 0.33 to 0.96], OR = 0.5 [0.25 to 0.97]), but there was no
 15 difference at 24 months and five-years. At five-years, odds of satisfaction with
 16 treatment lower was lower in the balloon group (OR = 0.13 [CI 0.02 to 0.94]), and
 17 complications were more likely with TBEA than REA. Duration of surgery was lower
 18 in the balloon group (WMD = 20.8 minutes [CI 19.2 to 22.5]). Other outcomes
 19 showed no differences at 12, 24 and 36 months.

20

21 *TBEA versus TCRE*

22 One RCT (n = 82) was identified. TBEA was quicker (WMD 13 minutes [CI 10.8 to
 23 15.2]), mean intra-operative blood loss lower (WMD - 81.8 [CI -70.3 to -93.3]), and
 24 satisfaction greater at 24 months (OR = 7.2 [CI 1.4 to 35.9]) when compared with
 25 TCRE.

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TBEA versus laser

One RCT (n = 70) was identified. Women having TBEA treatment had a significantly greater pain score than women in the laser group (WMD 32.7, 95% CI 23.7 to 41.7). At 12 months follow-up, women in the TBEA group had higher scores on the Euroquol 5D VAS than women in the laser group (WMD 5.3, 95% CI 0.11 to 10.6).

Bipolar electrode ablation versus TBEA

One RCT (n = 126) was identified. Amenorrhoea was more likely in the electrode group (OR = 7.4 [CI 3.8 to 14.4]), and women in the electrode group were more likely to be satisfied with treatment outcome at 12-months (OR = 3.0 [CI = 1.3 to 7.0]).

The authors concluded that “Endometrial ablation techniques continue to play an important role in the management of HMB. The rapid development of a number of new methods of endometrial destruction has made systematic comparisons between methods and with the 'gold standard' of TCRE difficult. Most of the newer techniques are technically easier than hysteroscopy based methods to perform. However, uterine perforation, which is the major complication of endometrial ablation, cannot be excluded without hysteroscopy. Overall, the existing evidence suggests that success rates and complication profiles of newer techniques of ablation compare favourably with TCRE, although technical difficulties with new equipment need to be ironed out“.

No additional or subsequent RCTs were identified. However, one subsequent publication from an RCT included in the systematic reviews above was available.

The RCT (n = 126) compared bipolar radio-frequency endometrial ablation and TBEA. The study found no differences between the groups on any of the SF-36 scores, Rotterdam symptom checklist or state-trait anxiety score. The study concluded that both methods of ablation significantly improve QoL.³⁴¹ [EI = 1+]

In addition, due to the debate within the GDG about the conclusions made by some of the reviews, it was necessary to assess the individual RCTs upon which they were based.^{104;105;246;341-364} The results of this review are reflected in the recommendations made by the GDG.

Additional comparative studies are also available in the evidence table.^{103;365-400}

10.3.2 Economic studies on endometrial ablation

One economic evaluation met the criteria for inclusion [details of the study are provided above].³³⁹ The evaluation compared MEA and TBEA with TCRE, RA and hysterectomy. A state-transition (Markov) model was used, and assumed a hypothetical cohort of 1000 patients for a period of ten years. The average age of a women entering the model was 42. TBEA dominates all other ablation techniques. When compared with MEA, TBEA gives a similar number of quality adjusted life years across the cohort (TBEA 8360.77, MEA 8360.70) but at a slightly lower cost (TBEA £1323925, MEA £1448470). When compared with TCRE, RA and TCRE and RA in combination, both TBEA and MEA produced more quality adjusted life years at a lower cost. When compared with hysterectomy, MEA and TBEA are both less costly but provide fewer quality adjusted life years. Hysterectomy results in

8774.34 quality adjusted life years at a cost of £2320512. The incremental cost-effectiveness ratio for hysterectomy compared with TBEA is £2410/QALY, and compared with MEA is £2108/QALY. The study concluded that hysterectomy is cost-effective compared to MEA and TBEA.

The robustness of the study results were tested in a sensitivity analysis. When comparing MEA and TBEA, the results were found to be sensitive to changes in the cost of each procedure, the time required to undertake each procedure and to aspects that impact the total number of QALYs accrued. When comparing MEA and TBEA to TCRE, RA and hysterectomy, the model was highly sensitive to the utility values associated with being well following ablation. The study recommends that results are interpreted with caution owing to the sensitivity of the model to the utility values used.

10.4 Endometrial thinning as pre-treatment before endometrial ablation

When the 1st generation methods were introduced many surgeons used pharmacological methods to thin the endometrium. This was done with the intention both to improve the quality of the view within the uterine cavity and to reduce the amount of tissue needing to be removed or destroyed, so as to treat the endometrial glands in the superficial myometrium.

10.4.1 Review of Endometrial thinning as pre-treatment before endometrial ablation

One systematic review was identified that examined use of endometrial pre-treatment prior to endometrial destruction. The review found that GnRH-a was

beneficial in terms of ease of surgery and the short-term outcome. The review found that Danazol was less effective than GnRH-a, and only slightly better than placebo. The review found that progestogens were no more effective than placebo, and less effective than either GnRH-a or Danazol. However, the review was not complete, with a number of papers waiting to be reviewed by authors at time of publication. ⁴⁰¹

[EL = 1+]

Information from individual RCTs included in the review can be found in the evidence table. ⁴⁰²⁻⁴⁰⁴

One RCT (n = 210) compared MEA undertaken in the post-menstrual phase to endometrial ablation undertaken with hormonal pre-treatment (danazol 200mg bd, depot Gosealin 3.6mg 5 weeks prior to surgery). The study found no difference between the groups in relation to women's outcomes (patient satisfaction at 12 months: post-menses = 92.5% vs. drug group = 88.4%. No statistical difference). ⁴⁰⁵

[EL = 1++]

A second RCT (n = 90) of women with menorrhagia showed that pre-treatment of danazol or decapetyl before HTA had no effect on outcome compared to no pre-treatment. In both pre-treatment and no pre-treatment groups 93% of women had normal or no bleeding after treatment. However, duration of procedure and the amount of distending medium used was greater in the control group (no statistical analysis undertaken by authors). ⁴⁰⁶ [EL = 1-]

A third RCT (n = 30) comparing pre-treatment with desmopressin 3.75mg at 4-6 weeks prior to treatment, against a control group receiving no treatment for women undergoing TBEA, found that there were no differences between the groups in terms of outcome (Patient satisfaction: Pre-treatment = 15 (88%), control = 11 (92%)). No major adverse events were reported in either group. The study concluded that pre-treatment had no effect on surgery.⁴⁰⁷ [EL = 1-]

A fourth RCT (n = 50) examining the use of Medroxy Progesterone Acetate (DMPA) pre-treatment for women undergoing endometrial resection found no difference in outcome or duration of procedure, but level of fluid deficit did favour the pre-treatment group (DMPA = 690.2 ml, Control = 476 ml, (p < 0.005)).⁴⁰⁸ [EL = 1-]

10.4.2 Economic studies on pre-treatment before endometrial ablation

A systematic review identified one study that met the inclusion criteria.⁴⁰⁹ The study examined retrospectively the results of a randomised trial (n=160) comparing pre-operative medical endometrial thinning in women undergoing endometrial ablation for menorrhagia. Treatments compared were Goserelin (GnRH-a) and Danazol for either four or eight weeks and outcomes were measured by the differential rate of amenorrhoea in women 24 weeks and two years following treatment. Costs were estimated from an NHS perspective. The trial found a clinically significant difference in rates of amenorrhoea at 24 weeks and two years follow-up, though the difference was only statistically significant at 24 weeks. The incremental cost per additional woman with amenorrhoea using goserelin when compared with danazol was estimated at £788. Under sensitivity analysis, incremental analysis gave results that ranged from Danazol dominating goserelin (i.e. it was less costly and more

1 effective), to an incremental result of £201 per additional woman with amenorrhoea
2 when treated with goserelin. These results should be interpreted with caution, given
3 the sample size, the number of women unavailable at long-term follow-up and the
4 issue of whether an appropriate outcome has been selected.

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6 One study (n=210) compared MEA performed during the post-menstrual phase in an
7 outpatient setting under local anaesthetic with standard MEA in a day-case setting
8 after drug preparation of the endometrium. Outcomes measured were acceptability
9 of, and satisfaction with, treatment. Health related quality of life was measured using
10 the SF-12 (version 1). There were no statistically significant differences in SF-12
11 scores, and utility values were not calculated. Mean costs to the health service of the
12 post-menses group were £444 and for the drug preparation group £568. Costs to the
13 woman were also measured, but there was no significant difference between the
14 post-menses (£190) and drug preparation (£199) groups.⁴⁰⁵

10.4.3 Evidence statement on endometrial ablation/resection

One systematic review and four subsequent RCTs showed that pre-treatment for endometrial ablation has limited effect on outcome, but improved operating conditions for surgeon.

Result from three reviews and one RCT shows that endometrial ablation and resection methods produced clinically relevant reductions in MBL, and are associated with improvements in quality-of-life. TCRE, MEA, TBEA and REA techniques appear to be largely equivalent to one another in terms of clinical outcome, although one RCT shows that MEA is superior to TCRE in terms of satisfaction at five-years follow-up. Endometrial ablation and resection techniques are marginally less effective than hysterectomy at improving MBL and quality-of-life. A significant proportion of women undergoing ablation or resection require further surgery compared to hysterectomy, which may impact on the results of the studies using intention-to-treat analysis. Inclusion criteria of RCTs showed that uterine fibroids < 3 cm in size were allowable.

Costs for microwave ablation are slightly more than for thermal-balloon ablation, with no meaningful difference in number of quality adjusted life years. Both MEA and TBEA are less costly and resulted in slightly more quality adjusted life years than either TCRE or REA ablation.

When compared to hysterectomy, both second-generation ablation techniques are less costly, but result in slightly fewer quality adjusted life years. The incremental

cost-effectiveness ratio for hysterectomy compared to second generation techniques is within acceptable limits for the NHS.

MEA performed in an outpatient setting under local anaesthetic compares favourably in terms of cost with standard MEA in a day-case setting after drug preparation of the endometrium.

10.4.4 GDG Interpretation of evidence for endometrial ablation/resection

In their interpretation of the evidence, the GDG placed a high value on women retaining their uterus and on the impact of surgery.

With regards to endometrial ablation, the GDG examined the individual comparison of techniques. In the majority of RCTs this showed techniques to be largely equivalent. However, in one recent long-term follow-up study it was shown that MEA was superior to TCRE in terms of women's satisfaction. The GDG felt this was an important result. In combination with the health economics results this led to a recommendation that second generation EA techniques should be considered before first generation techniques.

10.4.5 Recommendations on endometrial ablation/resection

Hysteroscopy should be undertaken post-dilation, pre-procedure when undertaking endometrial ablation. **[D(GPP)]**

Endometrial ablation should not be undertaken on women wishing to become pregnant at any time in the future. **[D(GPP)]**

Second generation ablation techniques (MEA, TBEA) should be considered ahead of first generation techniques (TCRE, REA). **[A]**

If a TBEA is being undertaken then endometrial thinning is not required. **[D(GPP)]**

If an MEA is being undertaken then scheduling of surgery for post-menstrual phase is an alternative to endometrial thinning. **[A]**

In women with HMB alone, with uterus no bigger than a ten week pregnancy, endometrial ablation methods should be considered preferable to hysterectomy. ^{xvii xviii}

[A]

Women must be counselled on the need to use effective contraception after endometrial ablation. **[D(GPP)]**

Ablative techniques should be undertaken under local anaesthetic where appropriate **[D(GPP)]**

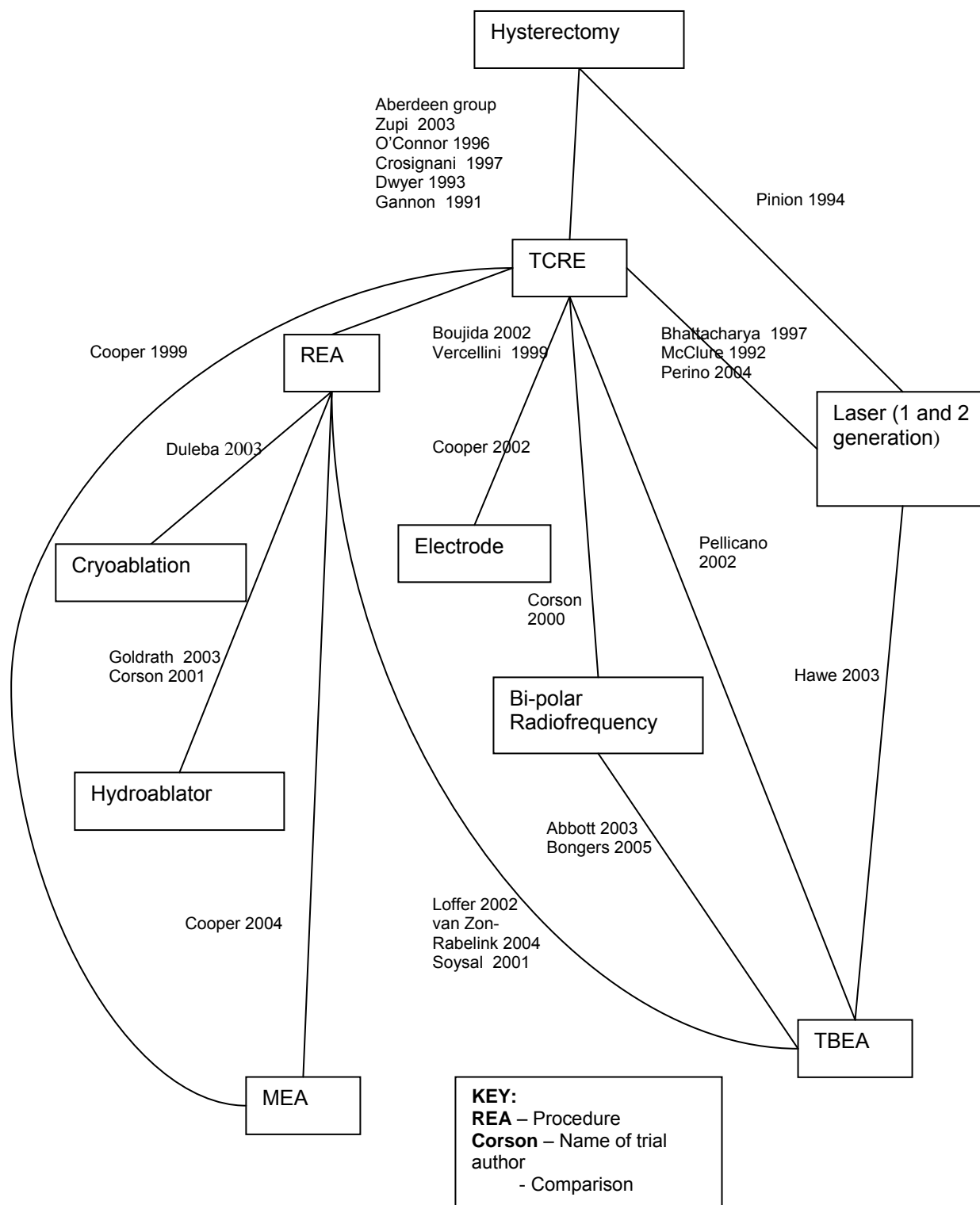
^{xvii} Reference should be made to the manufacturers own limits on uterus size.

^{xviii} It is recommended that the Medicines and Healthcare products Regulatory Agency (MHRA), safety notices on endometrial ablation should be followed (MDA [1998] SN 9812 Devices used for endometrial ablation achieved by thermal means, and MDA [1999] SN 1999(18) Devices used for endometrial ablation).

1 **10.4.6 Research recommendation for endometrial ablation**

- 2 Where evidence is not available on endometrial thinning prior to different ablative
- 3 techniques, then it is recommended this research be undertaken.

Figure 10.1 – Schematic of RCT comparisons undertaken for EA



References for figure 10.1 336;338;342-344;347-354;356;358;361-363;387;410-415

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11 Interventions for Uterine Fibroids.

Women with HMB associated with uterine fibroids have usually been offered hysterectomy as the only non-pharmacological treatment available. However, two alternative non-pharmacological treatments are available for the treatment of HMB in the presence of uterine fibroids.

Uterine artery embolisation (UAE) is an alternative treatment to hysterectomy for uterine fibroids. The procedure is performed under conscious sedation, and both uterine arteries are blocked with particles injected via the femoral and uterine arteries. This causes the fibroids to shrink, but is believed to have no permanent effect on the rest of the uterus. UAE is performed by an interventional radiologist.

Myomectomy is the surgical removal of fibroids. Myomectomy can be performed laparoscopically or hysteroscopically. However, choice of route is determined by the size and position of the fibroids(s). A concern with the use of myomectomy is that uterine fibroids will reappear and require further surgery.

11.2 Uterine Artery Embolisation

11.2.1 Review summary for treating HMB

Overview of available evidence

One systematic review of three RCTs was identified. One subsequent RCT was identified.

UAE versus hysterectomy

One review was identified (n = 3 RCTs) comparing UAE with hysterectomy or myomectomy. The review identified all the available RCT evidence on UAE. ⁴¹⁶ [EL = 1+]

In the RCT studies comparing UAE against hysterectomy, the review reported a shorter duration of procedure (WMD -16.40 minutes [95% CI -26.04 to -6.76]), less intra-procedure blood loss (WMD -405.20 ml [95% CI -512.71 to -297.69]), shorter length of hospital stay (WMD -3.27 days [95% CI -3.77 to -2.77]), and quicker resumption to normal activities (WMD -26.68 days [95% CI -36.15 to -17.21]) in the UAE group, compared with the hysterectomy group. There was no significant difference between the two groups in terms of need for blood transfusion (OR 0.04 [95% CI 0.00 to 0.33]), intra-procedural complications (OR 2.02, 95% CI 0.74 to 5.47), satisfaction with treatment (OR 0.47 [95% CI 0.09 to 2.48]) and unscheduled visits after discharge (OR 1.80 [95% CI 0.98 to 3.30]). However, readmission rates within 42 days favoured hysterectomy (OR 6.00 [95% CI 1.14 to 31.53]).

Further information on individual RCTs can be found in the evidence tables.⁴¹⁷⁻⁴²³

Economic evidence

One study was identified that met the inclusion criteria.⁴¹⁷ An economic evaluation was conducted alongside a clinical trial (n=157) comparing UAE with surgery (hysterectomy and myomectomy). Outcomes were expressed in terms of health related quality of life as measured by SF-36, EQ-5D and General Health Questionnaire 28 scores. Measurements were taken prior to treatment, at one month following treatment and 12 months following treatment. No statistically significant difference was detected using the SF-36 questionnaire after 12 months, and a cost minimisation analysis was conducted. This showed that UAE was less costly than surgery at 12 months, and is cost-effective from the perspective of the health service. UAE had a mean cost of £1685.36 (95% CI £1465.72 to £1905.00) compared to surgery at a mean cost of £2566.87 (95% CI £2263.73 to £2870.01). One-way sensitivity analysis demonstrated that the result is not sensitive to changes in cost.⁴¹⁷

UAE versus Myomectomy

In comparing UAE with myomectomy, the systematic review showed (one RCT) the results favoured UAE in the duration of procedure (WMD -34.50 minutes [95% CI -48.74 to -20.26]), length of hospital stay (WMD -1.60 days [95% CI -2.47 to -0.73]) and duration to full recovery (WMD -16.40 days [95% CI -21.16 to -11.64]). However, re-intervention rates favoured the myomectomy group (OR 8.97 [95% CI 1.79 to 44.95]). There was no significant difference between groups for febrile morbidity (OR 0.90 [95% CI 0.24 to 3.32]), need for antibiotics (OR 1.12 [95% CI

0.25 to 4.92]), need for blood transfusion (OR 0.21 [95% CI 0.01 to 4.48]), hospital stay one week (OR 0.11 [95% CI 0.01 to 2.08]), readmission to hospital (OR 2.29 [95% CI 0.20 to 26.58]) and total relief of all fibroid-related symptoms at six months follow-up (OR 0.36 [95% CI 0.12 to 1.11]).⁴¹⁶ [EL = 1+]

The review concluded that, “There is no evidence of benefit of UAE compared to surgery [hysterectomy or myomectomy] for satisfaction. The higher minor complications rate after discharge in the UAE group as well as the unscheduled visits and readmission rates require more longer term follow-up trials to comment on its effectiveness and safety profile”. The review highlights the limited amount of data available on this intervention, and due to the limited number of primary studies, much of the review is based on evidence from a single study, hence the wide confidence intervals for many outcomes.

One subsequent RCT (n = 157) on women who were referred for surgery due to uterine fibroids compared UAE against surgery (hysterectomy or myomectomy). At 12 months follow-up, the study found no difference between groups of SF-36 scores, EuroQol scores, complications or adverse events. However, the symptom score at 12 months was in favour of surgery (p = 0.0), as was need for subsequent treatment (13% vs. 4%).⁴¹⁷

Non-comparative studies

A prospective case series (n = 3160) of women who have undergone UAE examined reported adverse events. Major in-hospital complications occurred in 0.66% of women, and post-discharge major events occurred in 4.8% of women within the first

30 days of surgery. The number of in-hospital events reported, were: none event (n = 2952), 1 event (n = 89), 2 events (n = 5). Of these events, 20 were defined as major and 74 as minor. Post discharge adverse events (n = 2729) reported were: none (n = 2019), 1 event (n = 519), 2 events (n = 128), 3 events (n = 49), over 4 events (n = 14). Of these, 135 were defined as major events and 848 as minor events.⁴²⁴ [EL = 3]

Multivariate analysis showed that adverse events were significantly associated with the following factors: having had any prior procedure (OR 1.235, p < 0.001), DVT prophylactic use (OR 0.757, p = 0.005), duration of procedure: (OR 1.004, p = 0.009), African-American (OR 1.129 (p = 0.021)) and current or recent smoker (OR 1.141 (p = 0.039)). The study concluded that “Uterine embolisation for leiomyomata is a low-risk procedure with little variability in short-term outcome based on either patient demographics or practice setting”.⁴²⁴ [EL = 3]

A second study based on the same cohort of women as the above study (n = 2122 at baseline, n = 1798 at 6-months, n = 1701 at 12-months) reported a significant improvement in symptom score and HRQOL score from baseline to 12 months. Subsequent medical treatment, gynaecological interventions and unplanned ER or hospital visits were reported in 7.11%, 5.88% and 3.06% of women respectively at 12 months. Amenorrhoea as a result of UAE occurred in 7.3% of women and 82% of women were satisfied with their outcome.⁴²⁵ [EL = 3]

Multivariate analysis showed that a greater improvement in symptom and health-related quality-of-life scores 12 months after UAE was likely to be associated with

1 factors such as predominant presenting symptoms of HMB, leiomyoma size,
2 submucosal leiomyoma and age. The study concluded that “Uterine embolisation
3 results in substantial symptom improvement for most patients, with hysterectomy
4 required in only 2.9% of patients in the first 12 months after therapy”.⁴²⁵ [EL = 3]

5
6 Additional non-RCT studies can be found in the evidence table.⁴²⁶⁻⁴⁵³

11.3 Myomectomy

A number of routes (abdominal, vaginal, hysteroscopic and laparoscopic) are used to perform myomectomy. The choice of route is decided by the size of uterine fibroid, the location of uterine fibroid, the size and shape of the vagina and the training and experience of the surgeon.

11.3.1 Review on myomectomy for treating HMB

Overview of available evidence

No systematic reviews examining myomectomy for the treatment of HMB were identified. Two RCTs were identified, one comparing myomectomy against UAE, and another comparing different types of myomectomy. A number of comparative observational studies were also identified.

Abdominal myomectomy versus hysterectomy

A cohort study compared peri-operative morbidity between women who underwent abdominal myomectomy (AM) (n=197) or abdominal hysterectomy (n=197). It reported no significant difference in overall morbidity between the two groups (39% vs. 40%; OR 0.93 [95 CI 0.63 to 1.40]). There was significant lower prevalence of haemorrhage and performance of an unintended procedure in the myomectomy group than in the hysterectomy group. AM was a lengthier procedure but was associated with significantly less blood loss. The average hospital stay was significantly shorter in the myomectomy group. Overall, no clinically significant difference in peri-operative morbidity between myomectomy and hysterectomy was

detected. Myomectomy may be considered a safe alternative to hysterectomy.⁴⁵⁴

[EL = 2+]

Abdominal myomectomy versus uterine fibroid embolisation

One RCT comparing UAE against myomectomy was identified and was summarised in the UAE review. The results favoured UAE in the duration of procedure (WMD -34.50 minutes [95% CI -48.74 to -20.26]), length of hospital stay (WMD -1.60 days [95% CI -2.47 to -0.73]) and duration to full recovery (WMD -16.40 days [95% CI -21.16 to -11.64]). However, re-intervention rates (additional treatment for fibroids) favoured the myomectomy group (OR 8.97 [95% CI 1.79 to 44.95]). There was no significant difference between groups for febrile morbidity (OR 0.90 [95% CI 0.24 to 3.32]), need for antibiotics (OR 1.12 [95% CI 0.25 to 4.92]), need for blood transfusion (OR 0.21 [95% CI 0.01 to 4.48]), hospital stay one week (OR 0.11 [95% CI 0.01 to 2.08]), readmission to hospital (OR 2.29, 95% CI 0.20 to 26.58) and total relief of all fibroid-related symptoms at six months follow-up (OR 0.36, 95% CI 0.12 to 1.11). However, this RCT was based on preliminary results only.⁴¹⁶ {EL = 1+}

A cohort study (n=111) compared outcomes in women undergoing AM (n=44) or uterine artery embolisation (UAE)(n=97) for symptomatic fibroids. At 14 months follow-up, there was a significant reduction in menorrhagia in the UAE group (92% vs. 64%, p<0.05) but not in pain (52% vs. 74%, NS). Treatment of mass effect was significantly more successful in AM when compared with UAE (91% vs. 76%, p<0.05). Complications occurred in 25% and 11% of AM and UAE, respectively (p<0.05). Mean blood loss was 376 ml in the AM group and minimal in the UAE group. There were significant differences in mean hospital stay and mean days till

normal activity between the two groups (2.9 vs. 0 days and 39 vs. 8 days, respectively; $p < 0.05$). This study concluded that UAE is less invasive and a safer treatment than AM in women with symptomatic fibroids. {26414} [EL=2+]

A cohort study compared long-term outcomes of AM ($n=30$) and UAE (UAE) ($n=51$) in women with symptomatic fibroids. It reported that further invasive therapy was significantly more likely in the UAE group than the AM group (29% vs. 3%, OR 12.5 [95%CI 1.4 to 110.1]) at 3 to 5 years follow-up. Among women not needing further surgery, overall symptoms improved in 92% of UAE and 90% of AM. Ninety-four percent of the UAE group and 79% of the AM group were somewhat satisfied with their choice of procedure ($p=0.06$).⁴⁵⁵ [EL=2+]

Hysteroscopic myomectomy: with versus without endometrial ablation

This combined therapy is undertaken in order to control HMB; but undertaking endometrial ablation means that a woman's potential future fertility is reduced compared to myomectomy alone, where fertility is retained.

A cohort study compared control of bleeding between women undergoing hysteroscopic myomectomy with endometrial ablation ($n=73$) and women undergoing hysteroscopic myomectomy without endometrial ablation ($n=104$). The follow-up period was up to 15 years. Bleeding was controlled in 96% of women with endometrial ablation vs. 81% of women with no endometrial ablation (OR 0.18, 85% CI 0.05 to 0.63). Bleeding was controlled in 90% of women who had complete removal of myoma vs. 76% in women with incomplete removal of myoma (OR 0.39 [95% CI 0.16 to 0.99]). In women who had complete removal of myoma and

1 endometrial ablation: bleeding was controlled in 97% compared to 84% in women
 2 who had complete removal of myoma and no endometrial ablation (OR 0.19 [95% CI
 3 0.04 to 0.87]). In women who had incomplete removal of myoma, bleeding was
 4 controlled in 92% in those who had concomitant endometrial ablation, as compared
 5 to 70% in those women who had no endometrial ablation (OR 0.20 [95% CI 0.02 to
 6 1.79]). There was significant success in control of bleeding among women who had
 7 complete removal of myoma with endometrial ablation versus those who had
 8 incomplete removal of myoma with endometrial ablation (common OR 5.25 [95% CI
 9 1.49 to 18.54]). There were no significant differences in the rates of subsequent
 10 hysterectomy between all of these groups. Endometrial ablation at the time of
 11 hysteroscopic myomectomy improves results in the control of bleeding.⁴⁵⁶ [EL=2+]

13 A comparative retrospective chart review (n=156 women, 94 hysteroscopic
 14 submucous resection of uterine leiomyomas and 62 endometrial ablation with or
 15 without submucous resection) reported on the long-term effectiveness of these
 16 procedures. In women undergoing hysteroscopic submucous resection of uterine
 17 leiomyomas, 24.5% reported late post-operative problems (recurrent abnormal
 18 bleeding, uterine rupture and pain) and 84% had not required further surgery by 9
 19 years follow-up. Among the endometrial ablation group, 23% of women experienced
 20 recurrence of increased bleeding and 91% had not required further surgery at the six
 21 year follow-up.⁴⁵⁷ [EI = 2-]

23 *Abdominal myomectomy versus combined abdominal myomectomy and uterine*
 24 *depletion*

A non-randomised study compared outcomes of women who underwent myomectomy only (n =108, Group 1) or combined uterine depletion (double ligation of the uterine artery) and myomectomy (n=234, Group 2) for the treatment of symptomatic fibroids. Though the operation time was significantly shorter in Group 1 (55 minutes vs. 68 minutes, $p<0.001$), there was significant reduction in intra-operative blood loss in Group 2 (50 ml vs. 250 ml. $p<0.001$). At 16 months follow-up, fibroid recurred in 19% in Group 1 and none in Group 2 ($p<0.001$).⁴⁵⁸ [EL = 2+]

Abdominal versus laparoscopic myomectomy

An RCT compared laparoscopic (n = 66) and AM (n = 65) in women with subserosal or intramural myomas. It reported a significantly higher incidence of febrile morbidity ($>38.0^{\circ}\text{C}$) in the abdominal group than in the laparoscopic group (26.2% vs. 12.1%; $p<0.05$). The mean drop in haemoglobin was more pronounced in the abdominal group (2.17 ± 1.57 vs. 1.33 ± 1.23 ; $p<0.001$). There was no significant difference in mean operative times in the two groups but the post-operative hospital stay was shorter in the laparoscopic group.⁴⁵⁹ [EL = 1-]

A retrospective chart review compared the results of open myomectomy (n = 49) with those of laparoscopic myomectomy (n = 49). It reported lower morbidity and fewer complications in women undergoing laparoscopic myomectomy when compared with open myomectomy. The mean operative time was significantly shorter and mean blood loss higher in the open myomectomy group (133 minutes vs. 264 minutes and 340 ml vs. 110 ml, respectively). The mean hospital stay was shorter (5.6 vs. 0.6 days) and the overall frequency of adhesion was lower in the laparoscopic group.⁴⁶⁰ [EL = 3]

Hysteroscopic myomectomy

A case-series (n = 196) of women undergoing hysteroscopic myomectomy for haemorrhagic submucous fibroids reported a failure rate of 18% (13% subsequent hysterectomy and 5% had recurrent bleeding) at an average of 73 months follow-up. Symptomatic improvement was reported by 68% of women. Hysteroscopic myomectomy appears to be satisfactory over the long term with low complication rates.⁴⁶¹ [EL = 3]

A case-series study followed up women (n=108 women who underwent hysteroscopic resection of myomas) over seven years. It reported a cumulative rate of 34% in myoma recurrence and a cumulative probability of recurrent menorrhagia of 30% at 3 years. Hysteroscopic myomectomy gave satisfactory menorrhagic control and limited recurrence, but the effect on fertility is limited.⁴⁶² (EL = 3)

Additional information from non-comparative studies can be found in the evidence table.^{460;463-466}

Pre-operative medical treatment

One systematic review (20 RCTs) evaluated the role of pre-treatment with GnRH-a prior to hysterectomy or myomectomy for uterine fibroids. In these trials, women underwent either hysterectomy (abdominal or vaginal) or myomectomy (abdominal or laparoscopic). Where it was outlined, case selection in these RCTs indicated that only women with subserous/intramural myomas were included. The characteristics of the women at baseline indicated that uterine volume ranged from 300 to 1086 ml

and myoma size from 4.7 to 7.8 cm in diameter, 59 to 238 ml in volume (with uterine volume between 150 ml and up to 680 ml, or between 12-18 gestational weeks, or less than 4 myomas bigger than 4cm³ in diameter, or myomas less than 10cm in diameter, or fibroid size/volume up to 238 ml.).⁴⁶⁷ [EL = 1+]

Pre- and post-operative haemoglobin (Hb) and haematocrit (HCT) were significantly improved by GnRH analogue therapy prior to surgery, and uterine volume, uterine gestational size and fibroid volume were all reduced. The proportion of women with pelvic symptoms was significantly higher in the group with no GnRH-a pre-treatment (OR 2.1, 95 %CI 1.4 to 3.0). Improvement of dysmenorrhoea was significantly more likely in the GnRH-a group (OR 3.7, 95% CI 2.0 to 6.7). In the pre-treatment group, some adverse events such as hot flushes, vaginitis, sweating and change in breast size, were more likely during GnRH analogue therapy. Blood loss and rate of vertical incisions were reduced for myomectomy (WMD -67.5 ml, 95% CI -90.6 to -44.4). Evidence of increased risk of fibroid recurrence after GnRH analogue pre-treatment in myomectomy patients was equivocal and few data were available to assess change in post-operative fertility. The review concluded that the use of GnRH analogues for 3 to 4 months prior to fibroid surgery reduce both uterine volume and fibroid size.

Detailed information from the individual RCTs included in the review can be found in the evidence table.⁴⁶⁸⁻⁴⁷⁸

11.4 Other interventions for uterine fibroids

Limited evidence was found on other interventions for uterine fibroids, such as myolysis. However, the quality and amount of evidence available on any one treatment was too limited to make recommendations.

11.5 Evidence statement on interventions for fibroids

Evidence from one systematic review of RCTs, and a large number of observational studies, showed evidence that UAE improves HMB symptoms associated with uterine fibroids to a level equivalent to hysterectomy and myomectomy. However, readmission rates within 42 days favoured hysterectomy (OR 6.00; 95% CI 1.14 to 31.53), and the re-intervention rate favoured the myomectomy group (OR 8.97, 95% CI 1.79 to 44.95). Cost-effectiveness evidence from one study found no difference in quality of life scores at 12 months between UAE and surgical treatment arms. Costs for UAE were significantly lower than those for surgery. Evidence from two RCTs and several observational studies shows that myomectomy improves symptoms associated with uterine fibroids, and that different methods of myomectomy can be considered equivalent. Evidence was inconclusive about the advantages and disadvantages of myomectomy compared to other treatments.

GnRH-a use in myomectomy depends on size, number and site of uterine fibroids. In women with multiple small uterine fibroids, use of GnRH could hamper surgery, whereas in women with a single large uterine fibroid GnRH-a use could ease surgery.

11.6 GDG interpretation of evidence on interventions for uterine fibroids

The GDG placed a high value on women retaining their uterus and potential fertility when assessing the evidence.

The fact that MBL related symptoms were not always explicitly examined means that the GDG had to extrapolate the results for an HMB population. The GDG highlighted that the size and site of uterine fibroids is important in determining treatment. The GDG highlighted that in UAE, many variables defined as complications are often unavoidable results of treatment. There is insufficient evidence on long-term complication and reoccurrence rates to make recommendations on these issues. The GDG also highlighted that other techniques are becoming available within a research setting, such as myolysis

11.7 Recommendations on interventions for uterine fibroids

Prior to scheduling of UAE or myomectomy, the uterus and fibroid(s) should be assessed by imaging, preferably MRI when available. **[D (GPP)]**

UAE is recommended for women with HMB associated with uterine fibroids and who want to retain their uterus and/or avoid surgery. **[B]**

Use of GnRH-a should be stopped as soon as UAE has been scheduled. **[D (GPP)]**

Myomectomy is recommended for women with HMB associated with uterine fibroids and who want to retain their uterus. **[D]**

Women should be informed that UAE or myomectomy will potentially allow them to retain their fertility. [C]

11.8 Implementation advice for interventions for uterine fibroids

Both myomectomy and UAE are specialist interventions and in order for the recommendations outlined above to be implemented, then the appropriate training and experience is required by clinicians.

11.9 Research recommendations on interventions for uterine fibroids

- What effect do UAE and myomectomy have on long-term fertility of women?
- What are the psychosexual impacts on UAE and myomectomy?
- What are the long-term recurrence rates of fibroids after UAE or myomectomy?
- How does UAE effect blood flow in the uterus?
- What is the mechanism of action via which UAE reduces MBL?
- What is the ovarian function after UAE or myomectomy?
- What is the ovarian and uterine function of women with or without HMB?

12 Hysterectomy

Hysterectomy is defined as the "surgical removal of the uterus". It is one of the most common of all surgical procedures and can also involve the removal of the fallopian tubes, ovaries and cervix to cure or alleviate a number of gynaecological complaints. Hysterectomy was once considered the only suitable surgical treatment for women suffering with HMB. However, a number of treatments have emerged as alternatives to hysterectomy. This change in the management of HMB can be seen in the change in the number of hysterectomies undertaken for bleeding disorders in the UK, according to Hospital Episode Statistics (HES) (from 24355 in 1993 to 10559 in 2002). Clearly, this suggests that any debate about the use of hysterectomy for treatment of HMB is very different today than it was 10 years ago, when it was the primary non-pharmaceutical treatment.

Oophorectomy is the medical term for the surgical removal of the ovaries. Oophorectomy is undertaken when disease requires the ovaries to be removed, but is often undertaken as a prophylactic procedure to reduce the risk of cancer. In the case of HMB, oophorectomy is often undertaken as an incidental treatment to hysterectomy.

Both interventions represent major surgery requiring several weeks of physical recuperation by the women. The psychological impact of these interventions are less easy to quantify, but are likely to take at least as long as physical effects to recover from.

1

2 **12.2 Indications for hysterectomy**

3 Given that there are now a number of treatment options for HMB that do not
4 involve the removal of the uterus, it is important that the indications for the use
5 of hysterectomy are clearly defined. Indications for surgery should include the
6 consideration of physical, psychological and social factors.

7

8 **12.2.1 Review on indications for hysterectomy**

9 *Overview of available evidence*

10 One guideline and five observational studies were included in the review.

11

12 *Indications for hysterectomy*

13 One evidence based guideline on indications for hysterectomy stated that it
14 should only be considered in cases of DUB after investigations had been
15 undertaken to establish cause of bleeding, medical treatment had failed or
16 been refused by the woman, and the woman had been made aware of all
17 alternative treatment options. For situations where myomas were present the
18 indications were the same as for DUB, but prophylactic use of hysterectomy is
19 indicated if myomas are growing rapidly to a point where the outcome of
20 surgery may be affected.⁴⁷⁹ [2+]

21

22 A consensus statement (n = 17) based on a Delphi process undertaken with
23 17 gynaecologists, outlined the main indications for hysterectomy. In relation
24 to hysterectomy for HMB related symptoms, the study makes clear
25 recommendations: Hysterectomy should only be considered after thorough

1 investigation of cause of HMB; Surgery for DUB is only indicated when it is
 2 causing anaemia and major impairment; Surgery for myomas associated with
 3 HMB is indicated when it causes anaemia and/or major impairment. ⁴⁸⁰ [EL =
 4 4]

5

6 A prognostic study (n = 236) of women who underwent either hysterectomy or
 7 were treated with LNG-IUS showed that age and presence of fibroids did not
 8 affect outcomes at 12-months. However, presence of objective menorrhagia
 9 (>80 ml) did affect outcome, with those women who had menorrhagia having
 10 better outcomes with hysterectomy and those without menorrhagia having
 11 better outcomes with LNG-IUS. This suggests that the level of MBL should be
 12 assessed prior to surgery. ⁴⁸¹ [EL = 2+]

13

14 A patient preference study (n = 96) assessing women's reason for choosing
 15 treatment for HMB found that the majority of women were willing to accept a
 16 50:50 chance of treatment failure in order to avoid hysterectomy. ²⁴⁷ [EL = 3]

17

18 A second patient preference study (n = 180) identified women's main reasons
 19 for rejecting hysterectomy (the number one reason being – hysterectomy is a
 20 major operation), and that approximately 85% of women were willing to accept
 21 a 50:50 chance of treatment failure to avoid hysterectomy. ⁴⁸² [EL = 3]

22

23 A third patient preference study (n = 221) examined women's priorities from
 24 treatment for menorrhagia. The study that 'stops periods for good' and 'Back
 25 to usual activities as soon as possible' were the two most importance wishes

of women. These data show the dichotomy between women's wish to avoid hysterectomy and desire to stop menstrual periods.²⁴⁸ [EL = 3]

A fourth patient preference study (N = 23 focus groups) used qualitative to examine women's experience of undergoing hysterectomy. The study found that women try to avoid hysterectomy where possible, but when they do undergo surgery they are generally satisfied.⁴⁸³ [EL = 3]

A patient survey (n = 674) examined women's opinions on the advantages and disadvantages of hysterectomy. The main benefit of hysterectomy was seen as no further menstrual bleeding and the main disadvantage was early menopause.⁴⁸⁴ [EL = 3]

No RCTs examining prognostic factors or indications for hysterectomy were identified. However, RCTs examining therapeutic effect of different approaches to hysterectomy did outline criteria for surgery. The chief differentiation is between a vaginal route and an abdominal route to remove the uterus. The main factors involved in this decision are the size of the uterus (and any associated uterine fibroids) and the size and shape of the vagina. However, this is based upon only consensus.

12.2.2 Evidence statement on Indications for hysterectomy

Evidence from one systematic review and five observational studies are available. The systematic review states that investigations for causes of HMB, attempts at medical treatment and a full information provision for the

woman are required prior to hysterectomy. A consensus statement highlights that hysterectomy for HMB should only be undertaken after investigations to establish cause of HMB, failed medical treatment and a full information provision to the woman. In addition, hysterectomy is only indicated where HMB is causing anaemia and/or serious QoL impact. Patient preference studies show that women want certain outcomes for treatment for HMB, but also often want to avoid hysterectomy in order to achieve these outcomes. The inclusion criteria used for RCTs show that the size of uterus (and uterine fibroids) is the main clinical determinate of the route of the hysterectomy. However, due to differences in the measurement of uterine size there are no definitive cut-off points for route selection.

12.2.3 GDG Interpretation of evidence on for Indications for hysterectomy

The GDG placed a high value on women retaining their uteri, minimising the invasiveness of surgery, and patient choice.

12.2.4 Recommendations on Indications for hysterectomy

See section 12.4.3 for recommendations

12.3 Hysterectomy

A number of methods of hysterectomy are used by surgeons, but are based around three main routes of surgery: Abdominal hysterectomy (AH), vaginal hysterectomy (VH) and laparoscopic hysterectomy (LH). LH has three subdivisions: laparoscopic assisted vaginal hysterectomy (LAVH) where a vaginal hysterectomy is assisted by laparoscopic procedures that do not include uterine artery ligation, laparoscopic hysterectomy (LH(a)) where the laparoscopic procedures include uterine artery ligation, and total laparoscopic hysterectomy (TLH) where there is no vaginal component and the vaginal vault is sutured laparoscopically.

The decision about which route to use depends on the size of the uterus, the size of any uterine fibroids (large uterus and/or uterine fibroids make it more difficult to use less invasive techniques), the location of any uterine fibroids, the mobility of the uterus and the size and shape of the vagina.

12.3.1 Review of hysterectomy

Hysterectomy versus medical treatment

One RCT (n = 63) was identified that compared hysterectomy against further medical treatment in a population of women with AUB. The rate of continued vaginal bleeding at 24-months was 37% for medical treatment and 7% for hysterectomy (p < 0.001), with the continued bleeding in the hysterectomy group being due to cross-over between treatments arms. The hysterectomy

group had a significant reduction in symptoms, except for stress incontinence ($p = 0.34$) and urge incontinence ($p = 0.74$). The medical treatment group had significant reductions in symptoms for pelvic pain, pelvic pressure, and stress incontinence ($p < 0.05$) but all other changes were non-significant. By 24-months follow-up, 17 (53%) of the medical group had undergone a hysterectomy. The results suggest that after failed medical treatment, a hysterectomy produces better outcomes for women than further medical treatment. However, the results show that some women do benefit from further medical treatment and do not require a hysterectomy.^{121;331} [EL = 1+]

Hysterectomy versus LNG-IUS

One RCT ($n = 236$) was identified comparing hysterectomy with LNG-IUS for the treatment of HMB. The QoL results at 12 months showed that all measures improved for both groups (EQ-5D improved by 0.1 in both groups ($p=0.0001$) from baseline; SF-36 general health improved by 5.5 for IUS and 6.2 for hysterectomy from baseline). However, by 12 months follow-up, 24 of the LNG-IUS group had undergone hysterectomy, and a further 10 women had had LNG-IUS removed, while five women from the hysterectomy group had cancelled their operation.¹⁰⁷ The five-year follow-up showed no difference between interventions at five years, in terms of QoL.¹⁰⁶ However, a large proportion of the LNG-IUS group had undergone hysterectomy by five-years.¹⁰⁶ [EL = 1++]

In a separate analysis of different sub-groups ($n = 236$), neither presence of uterine fibroids nor age were predictors of outcome at 12-months for LNG-IUS or hysterectomy. A comparison of women with and without objective

1 menorrhagia (>80ml MBL) showed that in the LNG-IUS group women without
 2 menorrhagia had better QoL outcomes than women with menorrhagia on:
 3 anxiety ($p = 0.04$), EQ-5D ($p = 0.05$). In the hysterectomy group, women
 4 without menorrhagia had better outcomes than those with menorrhagia on:
 5 anxiety ($p = 0.007$), emotional well-being ($p = 0.01$) and energy ($p = 0.0002$).
 6 Women with menorrhagia had better outcomes with hysterectomy than LNG-
 7 IUS for: anxiety ($p = 0.003$), general health ($p = 0.04$), energy ($p = 0.05$), and
 8 pain relief ($p = 0.04$). Furthermore, multiple regression analysis showed that
 9 MBL was the most significant factor predicting outcome.⁴⁸¹ [EL = 2-]

10

11 *Hysterectomy versus endometrial ablation*

12 One systematic review (five RCTs) was found that compared hysterectomy
 13 and endometrial ablation. The review found that, in terms of reduction in
 14 MBL, hysterectomy provided greater reductions (At 12 months [3 studies, $n =$
 15 440] OR = 0.12 [0.06 to 0.25]). Patient satisfaction also favoured
 16 hysterectomy (At 12 months [3 studies, $n = 519$] OR = 0.46 [0.24 to 0.88], and
 17 at 24 months [3 studies, $n = 354$] OR = 0.31 [0.16 to 0.59]). However, quality
 18 of life measures (SF-36) showed no difference between groups, except for
 19 general health ($p = 0.02$), pain ($p = 0.007$), and social functioning ($p = 0.007$),
 20 that were all in favour of hysterectomy. Endometrial ablation techniques
 21 required less time to undertake, shorter hospital stays and fewer adverse
 22 events (duration of procedure between ablation/resection and hysterectomy [5
 23 studies, $n = 706$] WMD = -23.06 [95% CI -23.80 to -22.32] in favour of
 24 ablation/resection. Duration of hospital stay between ablation/resection and
 25 hysterectomy [5 studies, $n = 706$] WMD = -4.91 [95% CI -4.95 to -4.87] days

1 in favour of ablation/resection. Thirteen types of adverse events were
2 reported. Results favour ablation/resection over hysterectomy for eight of
3 these, five were no different). However, more women in the endometrial
4 ablation groups required further surgery within 12-months (5 studies, n = 706,
5 OR = 7.33 [95% CI 4.18 to 12.86]). The study concludes that
6 ablation/resection is an alternative to hysterectomy, but is less effective at
7 reducing MBL and improving satisfaction. However, ablation/resection does
8 lead to shorter duration of surgery and fewer complications.³³⁵ [EL = 1++]

9
10 One subsequent RCT (n = 203) compared TCRE against laparoscopic
11 hysterectomy. The study found that hysterectomy took longer (Operating
12 times: HER = 41.7 minutes, LSH = 71.5 minutes, p < 0.01), there was no
13 difference in complications, and by 2 year follow up, a higher proportion of the
14 TCRE group required additional surgery (TCRE = 12, LSH = 1). For QoL
15 outcomes (SF-36), there were significant improvements from baseline scores
16 for general health, social functioning, and for hysterectomy only in emotional
17 role and vitality. Furthermore, there were significant differences between
18 groups in favour of hysterectomy for general health, social function and vitality
19 scores (P< 0.01).³³⁸ [EL = 1+]

20
21 A sub-group analysis (n = 204) of an RCT already reported, found no
22 difference in ovarian or bladder function between ablation and hysterectomy
23 groups.³⁶⁵ [EL = 2+]

1 A five-year follow-up of a cohort study comparing hysterectomy and ablation
 2 (TCRE = 3845, hysterectomy = 3397, hysterectomy & BOS = 2305) found a
 3 higher loss of libido amongst women who had undergone hysterectomy or
 4 BOS (OR for loss of libido compared to TCRE for hysterectomy = 1.42 (1.22
 5 to 1.65), hysterectomy & BOS = 1.80 (1.51 to 2.14), $p < 0.001$), the same for
 6 loss of sexual arousal but not for vaginal dryness. The study concluded that
 7 at five-years follow up, women who had undergone hysterectomy reported an
 8 increase in psychosexual problems than those who had undergone TCRE,
 9 and these figures were higher for women who had had BOS at the time of
 10 hysterectomy.³⁸⁵ [EL = 2++]

11

12 This cohort study (n = 11323) shows that women undergoing hysterectomy
 13 have higher OR of developing urinary symptoms compared to women having
 14 TCRE, 5 years after surgery. Furthermore, the study shows that women
 15 undergoing LAVH have higher OR of developing urinary symptoms than those
 16 undergoing vaginal or abdominal hysterectomy.³⁸⁶ [EL = 2+]

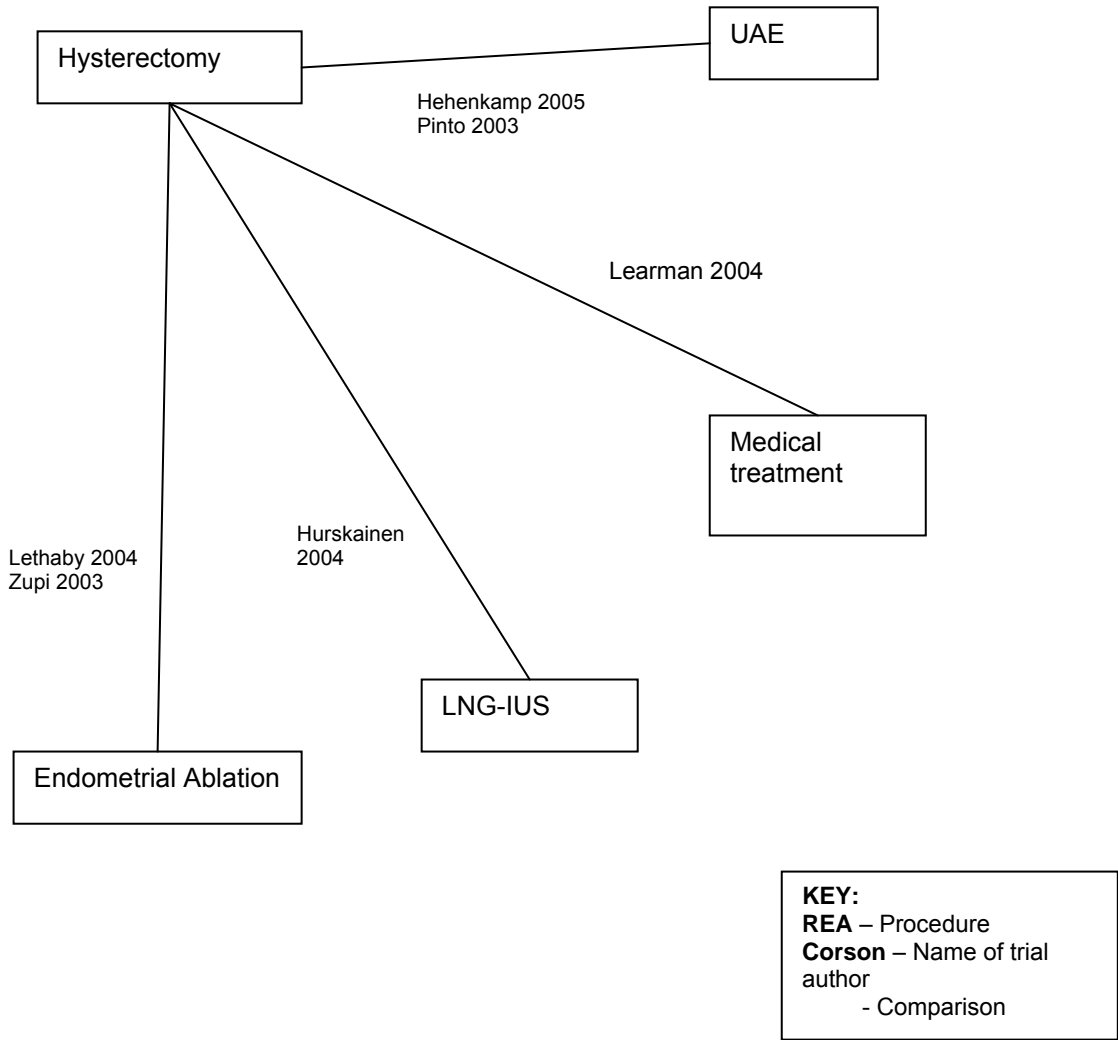
17

18 *Hysterectomy versus UAE*

19 A five-year follow-up of a cohort study comparing hysterectomy and ablation
 20 (TCRE = 3845, hysterectomy = 3397, hysterectomy & BOS = 2305) found a
 21 higher loss of libido amongst women who had undergone hysterectomy or
 22 BOS (OR for loss of libido compared to TCRE for hysterectomy = 1.42 (1.22
 23 to 1.65), hysterectomy & BOS = 1.80 (1.51 to 2.14), $p < 0.001$), the same for
 24 loss of sexual arousal but not for vaginal dryness. The study concluded that
 25 at five-years follow up, women who had undergone hysterectomy reported an

- 1 increase in psychosexual problems than those who had undergone TCRE,
- 2 and these figures were higher for women who had had BOS at the time of
- 3 hysterectomy. ³⁸⁵ [EL = 2++]

1 **Figure 11.1** - Schematic of RCT evidence for hysterectomy versus other
2 treatments 106;121;338;340;418;420



3

1 *Comparison of different routes of hysterectomy*

2 One systematic review (n = 27 RCTs, 3643 women) assessed the most
3 appropriate surgical approach to hysterectomy for women with benign
4 gynaecological conditions.⁴⁸⁵ [EL = 1++]

5

6 The review reported that the operation time for AH is significantly shorter than
7 LH (WMD 10.6 minutes, 95% CI 7.4 to 13.8). Statistical heterogeneity was
8 present for the operation time for LH versus AH (p-value = 0.00001), and that
9 VH has a significantly shorter operation time than LH (WMD 41.5 minutes,
10 95% CI 33.7 to 49.4). No results for AH vs. VH were presented.

11

12 The review assessed complication rates associated with the different routes
13 (see table 11.1 and 11.2). Where bladder and ureter injuries were pooled as
14 'urinary tract injury', there was a significant increase for LH versus AH (OR
15 2.61, 95% CI 1.22 to 5.60), but there were no statistically significant
16 differences in urinary tract injury for LH versus VH (OR 1.00, 95% CI 0.36 to
17 2.75) or for LH(a) versus LAVH (OR 1.60, 95% CI 0.29 to 7.83). There were
18 significantly fewer wound or abdominal wall infections (OR 0.32, 95% CI 0.12
19 to 0.85) and significantly fewer unspecified infections or occurrence of pyrexial
20 illness (OR 0.65, 95% CI 0.49 to 0.87) for LH vs. AH. There were significantly
21 fewer unspecified infections/febrile episodes in VH compared to AH (OR 0.42,
22 95% CI 0.21 to 0.83). Hospital stay was shorter (WMD 1.0 day, 95% CI 0.7 to
23 1.2) and return to normal activities sooner (WMD 9.5 days, 95% CI 6.4 to
24 12.6) in women undergoing VH when compared with AH.

25

1 Recovery was also shorter in the LH compared to AH (hospital stay WMD 2.0
2 days [95% CI 1.9 to 2.2]; return to normal activities WMD 13.6 days [95% CI
3 11.8 to 15.4]).⁴⁸⁵ Shorter recovery time from surgery favoured VH versus AH
4 in terms of shorter hospital stay (WMD 1.0 day [95% CI 0.7 to 1.2 days]) and
5 quicker return to normal activities (WMD 9.5 days [95% CI 6.4 to 12.6 days]).
6 There were no significant differences in recovery from surgery, in terms of
7 hospital stay or return to normal activities for LH versus VH, or in terms of
8 hospital stay for LH(a) versus LAVH.

9

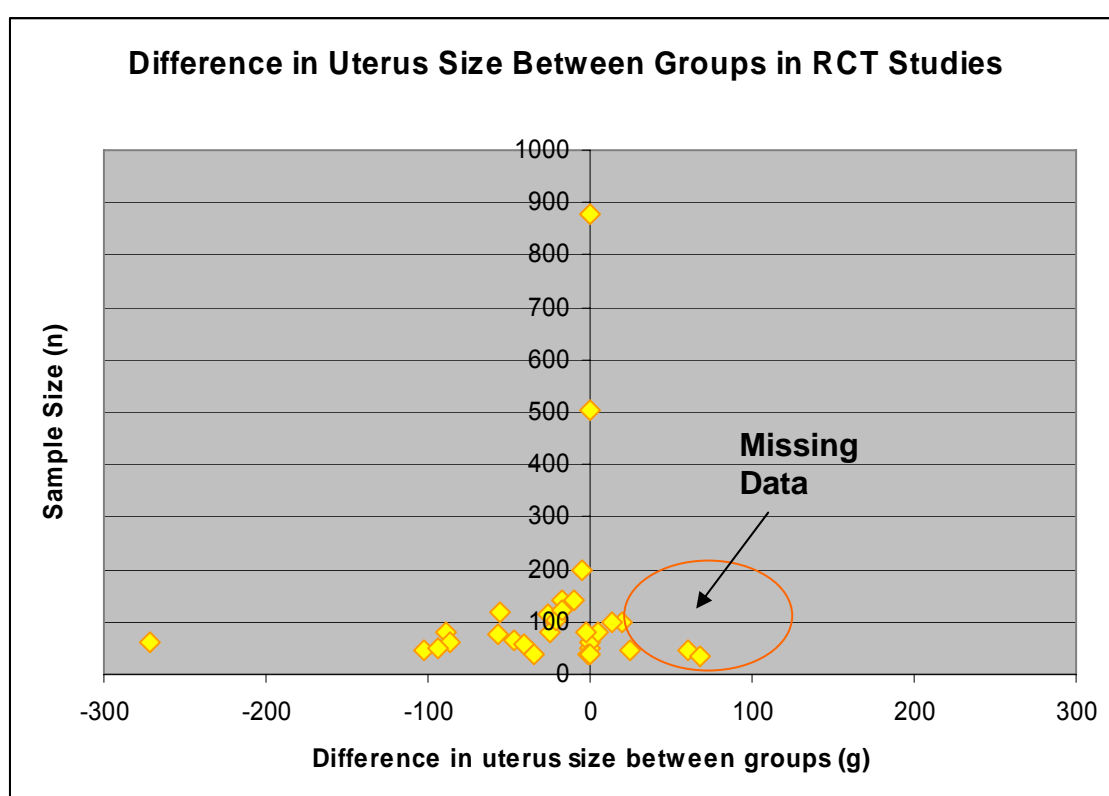
10 The study concluded “When technically feasible, VH should be performed in
11 preference to AH because of more rapid recovery and fewer febrile episodes
12 postoperatively. Where VH is not possible, LH has some advantages over AH
13 (including less operative blood-loss, more rapid recovery, fewer febrile
14 episodes and wound or abdominal wall infections) but these are offset by
15 longer operating time and more urinary tract (bladder or ureter) injuries. No
16 advantages of LH over VH could be found and LH operations took longer...
17 The surgical approach to hysterectomy should be decided by a woman in
18 discussion with her surgeon in light of the relative benefits and hazards”.

19

20 However, the majority of the evidence for hysterectomy is based on mixed
21 populations and therefore any results have to be extrapolated to an HMB
22 specific population. In addition, the systematic review did not assess if the
23 groups included in the RCTs were balanced at baseline. Analysis of baseline
24 characteristics (see figure below) showed that, on average, people in study
25 groups had a smaller uterine size compared to those in the control groups

(the plot includes means and median average; plus studies of women with large uteri, so only descriptive results are available). Whilst differences at baseline were only significant within one individual study, the overall effect appears to show a bias and this may impact on the interpretation of meta-analysis results.

Figure 11.2 - Bias in hysterectomy trials



In addition, the issue of surgeon training and experience have not been taken into account in the review, and many of the studies included in the review were undertaken to demonstrate that LH surgery could be undertaken in the presence of large uteri or fibroids. However, the degree of training and experience required to achieve these aims was not taken into account in analysis. The evidence base is also concentrated on the examination LH

techniques against VH and AH methods. This may mean an over emphasis in the evidence base on LH techniques.

Details of the RCTs included in the review can be found in the evidence table 486-513

A subsequent publication (n = 74) based on an RCT comparing LH against AH, already included in the review examined psychological well-being and found that both groups improved from baseline on a number of components, but neither on total score (baseline: LH vs. AH total score: 93.9 (SD 23.7) vs. 92.0 (SD 18.7), one year total score: 102.8 (SD 15.8) vs. 97.3 (SD 19.1)). There was no difference between the groups on psychological or psycho-sexual scores. This study implies that psychological well-being and sexuality after hysterectomy are not influenced by surgical technique. The numbers included in the study are different between the two publications; this appears to be due to the fact that not all patients were asked to complete the same information. In total 241 women were included in studies comparing LH and AH, and these were reported in several publications (not all included in this review).⁴⁹⁰ [EL = 1+]

One subsequent RCT (n = 30) on women (15 vaginal hysterectomy, 15 abdominal hysterectomy) compared AH against VH in women with benign gynaecological conditions. Duration of operation favoured AH (Vaginal = 85.3, abdominal = 69.1 (p < 0.0001)), length of stay (Vaginal = 3.1, abdominal

= 7.2 ($p < 0.0001$)) and tissue damage markers favoured VH. The study concluded that the methods were equivalent.⁵¹⁴ [EL = 1-]

12.3.2 Hysterectomy in presence of fibroids

The above review includes a number of studies where women with uterine fibroids were specifically included in the studies.

One RCT ($n = 119$) compared VH and AH in women with enlarged uteri. Based on these results the authors concluded that 'vaginal hysterectomy was a valid alternative to abdominal hysterectomy, even for large uterus'.⁵¹⁵ [EL = 1+]

12.3.3 Total versus sub-total hysterectomy

Three RCTs comparing total versus sub-total hysterectomy were identified. An RCT ($n = 319$) compared total hysterectomy against sub-total hysterectomy to treat benign gynaecological conditions. At 12-month follow-up, the study found a statistically significant difference between groups for urinary incontinence (total = 13 vs. subtotal = 24, OR = 2.08 [95% CI = 1.01 to 4.29], $p = 0.043$) in favour of total hysterectomy. However, there were no statistical differences between groups for quality of life (measured on SF-36), constipation, prolapse, satisfaction with sex life, pelvic pain, vaginal bleeding or complication rates.⁵¹⁶ [EL = 1+]

In a more detailed analysis of urinary tract symptoms the authors found that urinary incontinence was the only difference between groups at 12-months follow-up (13 vs. 25, $p = 0.03$), with all other urinary tract symptoms

(frequency; double/triple voiding; incomplete bladder emptying; nocturia; dysuria; urinary tract infection; stress incontinence; urge incontinence; mixed incontinence). In a multiple-regression analysis examining predictors of urinary incontinence after surgery, it was found that preoperative incontinence (OR = 11.2 [95% CI 5.1 to 25.9], $p < 0.0001$), operative method (OR = 0.43 [95% CI 0.18 to 0.96], $p = 0.044$), and size of uterus (OR = 1.56 [95% CI 1.00 to 2.49], $p = 0.051$) were predictors of urinary incontinence after surgery. Five other factors were not significant. Furthermore, the study found that urinary incontinence (OR = 463 [95% CI 69 to 3109], $p < 0.001$), frequency (OR = 29.2 [95% CI 4.1 to 211], $p = 0.001$) and incomplete bladder emptying (OR = 20 [95% CI 5.4 to 74.6], $p < 0.001$) were the main contributing factors to women being concerned about urinary symptoms. Other urinary symptoms were not significant predictors.⁵¹⁷

An RCT compared bladder, bowel and sexual functions, and post-operative outcomes between women undergoing subtotal hysterectomy ($n=133$) and total hysterectomy ($n=146$). It reported a significant reduction in urinary frequency (> 7 times a day) in the 2 groups at 12 months (33% in STH and 31% in TH before surgery vs. 24% and 20% respectively after surgery). The reduction in nocturia and stress incontinence and the improvement in bladder capacity were similar in both groups. There were no significant changes in bowel functions and sexual function in either group after surgery. Hospital stay was significantly shorter in the STH group than the TH group (5.2 days vs. 6 days; difference - 0.8 days [95% CI -1.6 to -0.04]). The rate of post surgery fever was significantly lower in the STH group (6% vs. 19%). After

1 STH, 7% of women had cyclical bleeding and 2% had cervical prolapse. ⁵¹⁸

2 [EL=1+]

3

4 One RCT compared surgical complications and clinical outcomes of women
5 undergoing total abdominal hysterectomy (n=67) vs. supra cervical
6 hysterectomy (n=68) for AUB due to benign causes. There was a significant
7 reduction in symptoms such as pelvic pain or pressure, back pain, urinary
8 incontinence and voiding dysfunction. There were no significant differences
9 between the two groups in the rates of complications, degree of symptom
10 improvement, hospital readmission or activity limitation. There was a
11 significant association between baseline body weight of >100kg and hospital
12 readmission (RR 2.18 [95% CI 1.06 to 4.48]). ⁴⁹⁷ [EL=1+]

13

14 The same RCT also assessed sexual functioning after SCH and TAH. It
15 reported a similar improvement in both groups during the first six months after
16 surgery, but it had stabilised by 1 year. There was no significant difference in
17 the mean score on the Sexual Function Scale in the two groups (82 in the
18 SCH group vs. 80 in the TAH group on a 0-100 scale with 100 indicating an
19 absence of problems; difference +2 [95% CI -8 to +11]) at 2 years. ⁵¹⁹ [EL=1+]

20

21 These results indicate that complications and adverse events are similar with
22 total and subtotal hysterectomy. Therefore, the decision about which method
23 to use should be based on other criteria.

24

25 *Observational studies*

1 Given the availability of RCT evidence on hysterectomy, the need to examine
2 observational studies is reduced. However, what observational studies
3 provide is long-term outcome data, which is especially important where major
4 surgery is undertaken, and it is for this reason that they are included. A
5 summary of the complication rates for the different types of hysterectomy,
6 found by the observational and RCT studies, is shown in tables 2 and 3.

7
8 A UK case series study (n=37295 cases of hysterectomies) reported that
9 complications occurred peri-operatively and post-operatively in 3% and 1% of
10 women undergoing hysterectomy. Hysterectomy for fibroids was associated
11 with significantly more complications than women with DUB (adjusted OR
12 1.34 [95% CI 1.14 to 1.56]). LAVH doubled the risk of operative
13 complications of AH (adjusted OR 1.92 [95% CI 1.48 to 2.50]). Both VH and
14 LAVH techniques had significantly higher risk of complications than AH
15 (adjusted OR 1.39 [95% CI 1.01 to 1.90] and adjusted OR 1.64 [95% CI 1.00
16 to 2.68] respectively). A reduction of risk was associated with increasing age
17 in women undergoing hysterectomy for fibroids, but not DUB. 14 deaths were
18 reported within the six-week period following surgery.^{520;521} This study
19 represents the best available evidence on complication rates for hysterectomy
20 within the UK. Only 45% of hysterectomies were reported to this study.
21 Analysis of a proportion of women not reported to the study suggests a three
22 fold higher rate of complications.³⁸⁵ [EL= 3]

23
24 A retrospective review of medical records of women undergoing hysterectomy
25 (n=1940) for benign and non-obstetric indications, over a 10 year period,

1 reported an overall mortality rate of 1.5/1000 women. The overall
2 complication rates were 44% for AH and 27.3% for VH, and unintended major
3 surgical procedures were required in 3% and 1% of AH and VH respectively.
4 The AH group was four times more likely than the VH group to require
5 surgical intervention (36% vs. 9%) at readmission. VH was associated with a
6 lower febrile morbidity and minor complication rate. Prophylactic antibiotics
7 significantly reduced the febrile morbidity by 50% and 40% of VH and AH
8 respectively.⁵²² [EL= 3]

9

10 A review of hysterectomy studies (n = 3112 LAVH, 1618 TAH, 690 VH from
11 34 studies) examined the reported complication rates. The review reported
12 higher complication rates for LAVH compared to TAH for bladder, ureter and
13 bowel trauma, fistula, and pulmonary embolus, but lower rates of sepsis and
14 transfusion. However, the study highlighted that differences in data collection
15 between studies could impact on results.⁵²³ [EL = 3]

16

17 A case note review of women undergoing hysterectomy (n=1299) reported a
18 significant reduction in symptoms severity (vaginal bleeding, pelvic pain, back
19 pain, activity limitation, sleep disturbance, fatigue, abdominal bloating, urinary
20 incontinence) and significant improvement in psychological function and
21 quality of life at two years after hysterectomy. There was a significant
22 association between lack of symptom relief and women who were in therapy
23 for depression at the time of hysterectomy (OR 3.45, 95% CI 1.84 to 6.51)
24 and in women with low income (OR 0.37, 95% CI 0.24 to 0.59) at two years.
25 Women who had bilateral oophorectomy at the time of hysterectomy were

significantly more likely to report symptom relief at two years (OR 2.01, 95%CI 1.14 to 3.53), but not at one year after hysterectomy.⁵²⁴ [EL=3]

12.3.4 Health Economics

One evaluation (n = 1380) compared vaginal and abdominal hysterectomy with a laparoscopic hysterectomy procedure in women with gynaecological symptoms that indicated hysterectomy. In this evaluation, laparoscopic hysterectomy cost on average £401 more and generated an additional 0.0015 QALYs than vaginal hysterectomy. This gives an incremental cost-effectiveness ratio for the base case analysis of £267,333. The sensitivity analysis found that at no level of willingness-to-pay for a QALY, is laparoscopic hysterectomy more than 50% likely to be cost-effective when compared with vaginal hysterectomy. Laparoscopic hysterectomy also cost more (£186) and generated more QALYs (0.007) on average than abdominal hysterectomy. The incremental cost-effectiveness ratio in the base case analysis was calculated as £26,571, although the sensitivity analysis concludes that at a maximum willingness-to-pay per QALY of £30,000, the probability that laparoscopic hysterectomy is cost-effective compared to abdominal hysterectomy is 56%.⁵²⁵

One study (n = 200) compared laparoscopic hysterectomy with abdominal hysterectomy only.⁴⁹⁸ This study found that the length of time required for laparoscopic hysterectomy procedures was longer than for abdominal hysterectomy (81 minutes (SD 30) and 47 minutes (SD 16) respectively, p<0.001). Laparoscopic hysterectomy was associated with shorter hospital

1 stay (4 days versus 6 days). There was no difference between the rate of
2 recovery and patient satisfaction of either treatment. Laparoscopic
3 hysterectomy cost more on average than abdominal hysterectomy (£2112
4 versus £1667). Because no differences were reported in EQ-5D analogue
5 scale scores, an incremental cost-effectiveness ratio was not calculated. It is
6 concluded that because there is no difference in clinical outcomes, patient
7 reported outcomes or patient reported quality of life, laparoscopic
8 hysterectomy is unlikely to be cost-effective compared with abdominal
9 hysterectomy.

10
11 One study (n = 80) compared laparoscopic hysterectomy and abdominal
12 hysterectomy where bilateral salpingo-oophorectomy was indicated in all
13 participants. This study found that laparoscopic vaginal hysterectomy (£1260)
14 was less costly than abdominal hysterectomy (£1750). Confidence intervals
15 for the costs were not presented. Laparoscopic vaginal hysterectomy took
16 longer to perform (100 minutes (SD 5.6)) than abdominal hysterectomy (57
17 minutes (SD 4.7)) ($P < 0.0001$). However, women who underwent
18 laparoscopic hysterectomy had shorter length of stay in hospital (3.5 and six
19 days, respectively, $p < 0.0001$), quicker recovery from pain (13 days and 26
20 days, $p < 0.0001$) and quicker return to work (21 days and 42 days, $p < 0.0001$).
21 Although laparoscopic surgery is more costly to perform, the difference in total
22 cost between methods is explained by earlier discharge from hospital.
23 Additional benefits may accrue to the woman through quicker post-operative
24 recovery and return to work.⁵⁰⁴

12.3.5 Evidence statement for hysterectomy

Evidence from one systematic review, five RCTs and five observational studies comparing hysterectomy against other treatments (LNG-IUS, UAE, or Endometrial Ablation) shows that hysterectomy is a highly effective treatment for the management of HMB. The systematic review of hysterectomy against endometrial ablation found that patient satisfaction favoured hysterectomy (At 12 months [3 studies, n = 519] OR = 0.46 [0.24 to 0.88], and at 24 months [3 studies, n = 354] OR = 0.31 [0.16 to 0.59]).

Evidence from one systematic review of RCTs, one subsequent RCT and four large non-comparative studies compare the different routes of hysterectomy. The data suggests that vaginal hysterectomy should be the preferred route of operation, as it has advantages over the abdominal route in terms of quicker recovery (Hospital stay [WMD 1.0 day, 95% CI 0.7 to 1.2] and return to normal activities [WMD 9.5 days, 95% CI 6.4 to 12.6] in women undergoing VH when compared with AH), and the vaginal route is preferred to laparoscopic surgery based on cost-effectiveness. However, the vaginal route is not suitable in all cases, as large uterus size, presence of pathology and low uterus mobility are all contraindications to the vaginal route being used. This is shown in the table of inclusion and exclusion criteria.

In those studies where not all women were indicated for oophorectomy, costs for laparoscopic hysterectomy were higher, on average, than for either vaginal hysterectomy or abdominal hysterectomy. One study that only included women that were indicated for bilateral salpingo-oophorectomy found

1 laparoscopic hysterectomy to be less costly than abdominal hysterectomy.
2 One study was of high quality and measured outcomes in QALYs. In this
3 study, the size of the difference between the costs was large in comparison to
4 the difference in outcomes measured in QALYs. Laparoscopic hysterectomy
5 is not likely to be cost-effective when compared with vaginal hysterectomy at
6 any level of willingness-to-pay per QALY. When compared with abdominal
7 hysterectomy, laparoscopic hysterectomy is unlikely to be cost-effective below
8 the NICE threshold of £20,000 per QALY. No direct cost-effectiveness
9 comparisons were made between vaginal and abdominal hysterectomy.

11 Hysterectomy undertaken for uterine fibroids was associated with significantly
12 more post-operative complications than women with DUB (adjusted OR 1.46,
13 95% CI 1.10 to 1.95). Evidence from three RCTs shows that where
14 abdominal hysterectomy is indicated, sub-total hysterectomy was associated
15 with higher rates of urinary incontinence than total hysterectomy, but had
16 quicker recovery times than total hysterectomy, and was equivalent to total
17 hysterectomy on all other measures.

19 **12.4 Pre-treatment for hysterectomy**

20 Pre-treatment before hysterectomy is often recommended in situations where
21 uterine fibroids are present. The rationale is that pre-treatments, such as
22 GnRH, reduce the size of fibroids, make surgery easier and even allow for the
23 less invasive vaginal route to be used.

12.4.1 Review of pre-treatment for HMB

One systematic review (26 RCTs) was found that assesses endometrial pre-treatment prior to hysterectomy or myomectomy for uterine fibroids. Where it was outlined, case selection in these RCTs indicated that only women with subserous/intramural myomas were included. The characteristics of women at baseline indicated that uterine volume ranged from 300 to 1086 ml, and myoma size from 4.7 to 7.8 cm in diameter and 59 to 238 ml in volume (with uterine size/volume between 150 ml and up to 680 ml, or between 12-18 gestational weeks, or less than 4 myomas bigger than 4cm³ in diameter, or myomas less than 10cm in diameter, or fibroid size/volume up to 238 ml).⁴⁶⁷

[EL = 1+]

Pre and post-operative haemoglobin (Hb) and haematocrit (HCT) were significantly improved by GnRH analogue therapy prior to surgery, and uterine volume, uterine gestational size and fibroid volume were all reduced. Pelvic symptoms were also reduced. However, some adverse events were more likely during GnRH analogue therapy. Hysterectomy appeared to be easier after pre-treatment with GnRH analogue therapy; there was reduced operating time and a greater proportion of hysterectomy patients were able to have a vaginal rather than an abdominal procedure. Duration of hospital stay was also reduced. Blood loss and rate of vertical incisions were reduced for both myomectomy and hysterectomy. The review concluded that the use of GnRH analogues for three to four months prior to fibroid surgery reduce both uterine volume and fibroid size. However, this review included both hysterectomy and myomectomy studies, and examined uterine fibroids rather

1 than HMB. Therefore, the results of this review can only be applied to women
2 with HMB in the presence of uterine fibroids.

3
4 An RCT (n = 188) excluded from review, compared Nafarelin nasal spray
5 against placebo, in women with uterine fibroids scheduled for hysterectomy.

6 The study found that at three-months, the uterus size on the Nafarelin group
7 was on average 23.7% smaller and in the placebo group 14.2% larger (p, <
8 0.001 from baseline, p < 0.05 between groups). However, adverse events
9 were higher in the Nafarelin group (Nafarelin = 107, placebo = 59).⁵²⁶ [EL = 1-

10]

11
12 A subsequent RCT (n = 51) was identified comparing leuprorelin against a
13 control group for hysterectomy in women with DUB. The study found no
14 statistical differences between groups for operative issues, complications or
15 patient outcomes, probably due to the small sample size.⁵²⁷ [EL = 1-]

1
2 **Table 11.1** - Results from long-term cohort studies

3

Complication	Abdominal Hysterectomy	Vaginal Hysterectomy	Laparoscopically Assisted Vaginal Hysterectomy Laparoscopic Hysterectomy Total Laparoscopic Hysterectomy
Death	0.38 per 1000 (0.25 to 0.64) within 6 weeks. RR 0.823 (0.733 to 0.926) within 5-years		
Major operative complications (%)	3.6	3.1	6.1
Major post-operative complications (%)	0.9	1.2	1.7
Urinary incontinence – moderate (OR)	1.19 (1.00 to 1.41)	1.30 (1.15 to 1.46)	1.82 (1.28 to 2.59)
Urinary incontinence - severe (OR)	1.52 (1.20 to 1.93)	1.59 (1.34 to 1.89)	2.02 (1.32 to 3.07)
Urinary frequency – moderate (OR)	1.28 (1.08 to 1.52)	1.10 (0.97 to 1.23)	1.03 (0.74 to 1.43)
Urinary frequency - severe	1.51 (1.20 to 1.90)	1.15 (0.96 to 1.37)	1.33 (0.85 to 2.07)

(OR)			
Nocturia – moderate (OR)	1.34 (1.06 to 1.69)	1.19 (1.01 to 1.39)	1.03 (0.68 to 1.57)
Nocturia - severe (OR)	1.33 (1.08 to 1.64)	1.17 (1.00 to 1.36)	0.90 (0.57 to 1.41)

1

1
2 **Table 11.2** - Results from RCT included in Cochrane review

Complication	Abdominal Hysterectomy	Vaginal Hysterectomy	Laparoscopically Assisted Vaginal Hysterectomy Laparoscopic Hysterectomy Total Laparoscopic Hysterectomy
Blood Transfusion (%)	3.33	3.87	4.23
Bowel injury (%)	0.67	0.00	0.20
Vascular injury (%)	0.77	0.94	1.81
Pelvic hematoma (%)	6.00	4.04	3.94
Vaginal cuff infection (%)	2.06	1.93	4.15
Would abdominal wall infection (%)	7.38	0.00	1.92
Laparotomy (%)	-	2.66	4.17

UT injury (bladder or urethral) (%)	0.86	1.60	2.33
Bleeding (%)	1.57	0.00	0.37
UTI (%)	4.87	1.27	4.77
Chest infection (%)	4.55	6.67	0.56
Infection unspecified (includes febrile morbidity) (%)	13.15	7.73	10.01
Thromboembolism (%)	0.00	0.00	0.59

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12.4.2 GDG interpretation of evidence on hysterectomy

The GDG placed a high value upon avoiding surgery and minimising the severity of surgery.

Due to the fact that hysterectomy stops any further menstrual bleeding, the GDG focused on QoL outcomes in order to compare hysterectomy against other treatments.

There were a number of concerns relating to applying the evidence base for the route of hysterectomy to an HMB population.

- Firstly, the populations in the studies included any benign gynaecological condition and therefore were not directly applicable to HMB.
- Secondly, evidence was found of a systemic bias towards smaller uterine size in test groups, compared to control groups. This may result in an over estimation of any benefits of test interventions.
- Thirdly, the evidence base was skewed towards investigation of laparoscopic hysterectomy, suggesting a bias amongst researchers towards the investigation of this technique.
- Finally, few studies took into account the training and learning curves associated with any of the techniques, or that surgery was undertaken by leading experts in particular techniques. Therefore, GDG interpretation of the available evidence took into account these issues when making recommendations.

12.4.3 Recommendations on hysterectomy

Hysterectomy should be considered only where:

- Other treatment options have failed or are inappropriate,
- Women have completed their families,
- There is a wish for amenorrhoea,
- And either women (who have been fully counselled) request it or other forms of further treatment are contraindicated. **[C]**

The route of hysterectomy to be used should be considered in the following order: first line, vaginal; second line, abdominal; and third line, laparoscopic.

[A]

Individual patient assessment is essential when deciding route of hysterectomy. Factors that need to be taken into account are:

- presence of other gynaecological conditions or disease,
- uterine size,
- presence and size of uterine fibroids,
- mobility and descent of uterus,
- size and shape of vagina,
- and history of previous surgery. **[D(GPP)]**

Any counselling should include: psychosexual impact, fertility impact, bladder function, need for further treatment, success rates (by patient), treatment complications, patient expectations, alternative surgery. **[D(GPP)]**

1

2 When abdominal hysterectomy is decided upon then both total and sub-total
3 methods should both be discussed with the woman. **D[(GPP)]**

4

5 Pre-treatment before hysterectomy and myomectomy with GnRH-a for 3 to 4
6 months should be considered where uterine fibroids resulting in an enlarged
7 or distorted uterus are present. ^{xix} **[A]**

8

9 Women should be informed about the increase in complications with
10 hysterectomy when uterine fibroids are present. **[C]**

11

12 When surgery for fibroid related HMB is felt necessary then myomectomy,
13 UAE and hysterectomy must all be considered, discussed and documented.
14 **[D(GPP)]**

15

16

^{xix} Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of GnRH-a is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented within the notes.

1

2 12.4.4 Implementation advice for hysterectomy

3 Hospitals should offer all types of hysterectomy in order for women to have
4 choice. This requires that surgeons with the training and experience to
5 undertake each type of surgery are accessible. Given that the number of
6 hysterectomies performed for menstrual disorders has more than halved in
7 the past ten years, consideration should be given to specialist training in
8 hysterectomy for HMB.

9

10 12.4.5 Research recommendations for hysterectomy

11 An investigation into the medium and long-term outcomes of subtotal and total
12 hysterectomy.

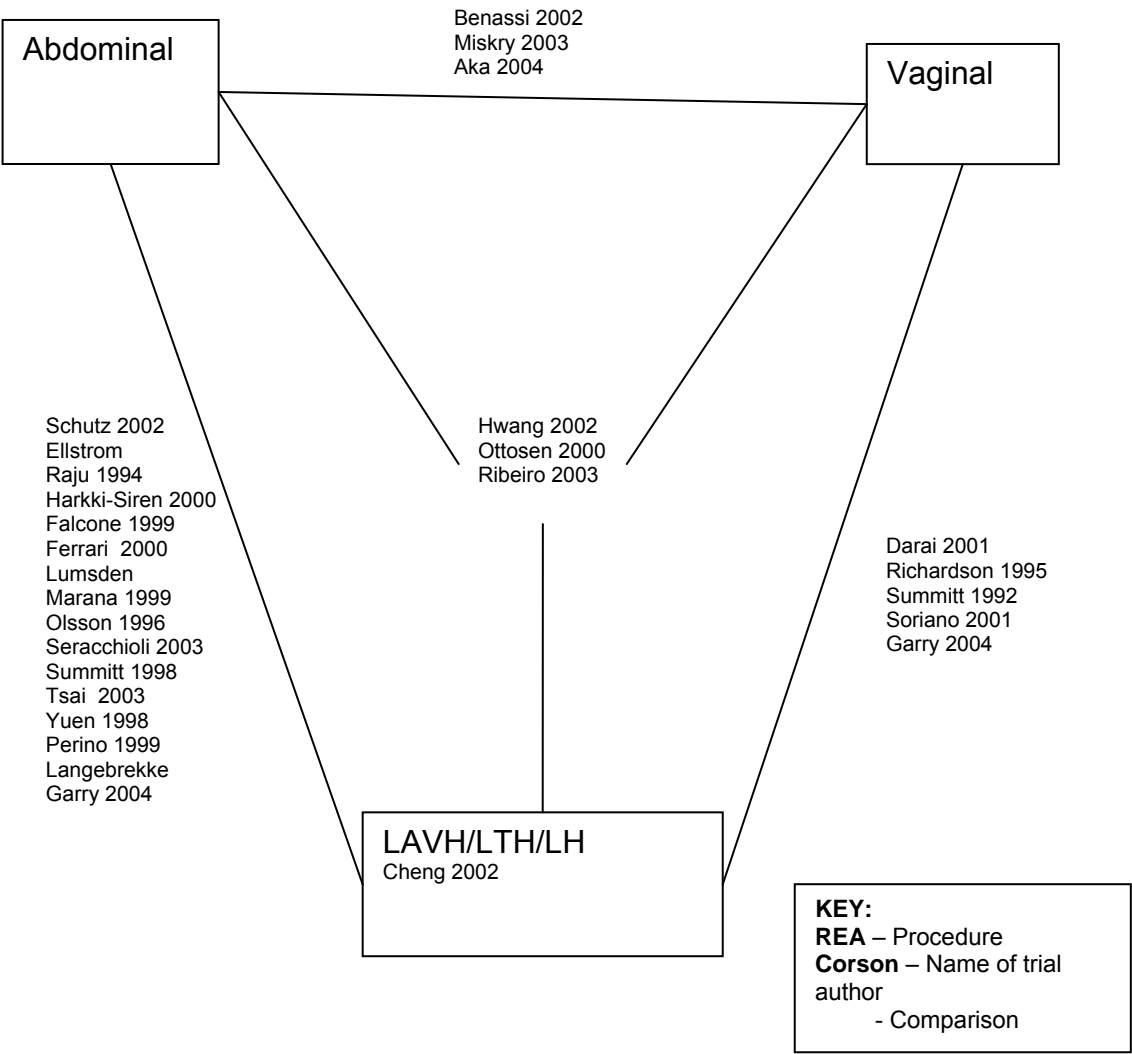
13 An investigation into the effect of hysterectomy and oophorectomy on cancer?

14

1

2 **Figure 11.4** - Evidence base for comparisons of routes of hysterectomy

3 486;487;490-492;494-496;498-512;514;515;525;528



4

1

2

3 **NOTE: A table will appear here summarising the outcome data for each**

4 **surgical and radiological treatment.**

13 Removal of ovaries at time of hysterectomy

Removal of the ovaries or oophorectomy is a common incidental surgery undertaken at the time of hysterectomy. The evidence relating to issues around oophorectomy on women undergoing hysterectomy for the treatment of HMB are examined below. Issues that need to be considered are: indications for surgery, and long-term impact of surgery, such as use of HRT.

13.2 Oophorectomy and HMB

No studies were identified linking HMB and the need for oophorectomy.

13.3 Prophylactic oophorectomy for prevention of cancer

A number of studies were identified relating to the prophylactic use of oophorectomy for prevention of cancer.

The argument for oophorectomy, and specifically prophylactic surgery at the time of hysterectomy for HMB, is the prevention of ovarian cancer and reduction in risk of breast cancer (based on rates from 2000-2002 from the USA, 1.48% of women born today will be diagnosed with cancer of the ovary at some time during their lifetime; see table 4). Information on this is published elsewhere.⁵²⁹⁻⁵³⁶ Women with genetic BRCA1 or BRCA2 mutations are at greater risk of ovarian and breast cancer.^{537;538} [EI = 3, EI = 3]

1 Retrospective studies looking at prophylactic oophorectomy at the time of
2 vaginal hysterectomy have shown that the ovaries can be removed
3 successfully in 65-97% of patients.^{539;540} [EL = 2-, EL = 2+] One case-series
4 found no significant increase in operating time, estimated blood loss, length of
5 hospital stay or postoperative morbidity between patients who had their
6 ovaries removed and those who did not.⁵³⁹ [EL = 2-] Another case-series
7 found that oophorectomy added 23.4 minutes to the total operating time
8 compared with vaginal hysterectomy alone.⁵⁴⁰ [EL = 2+]

9

10 The retrospective case control study investigated women who had chosen
11 prophylactic oophorectomy at time of hysterectomy instead of prolonged
12 screening and suggested that these women may have more physical and
13 emotional symptoms than women who remain on an ovarian cancer screening
14 programme, but that they report equivalent levels of cancer worry.²⁵⁶ [EL = 3]

15

16 A qualitative study (n = 16) found that women who want to retain their ovaries
17 had diametrically opposite opinions to those women who wanted
18 oophorectomy. Women who wanted to retain ovaries view them as a healthy
19 organ that does not need removing, while women who wanted oophorectomy
20 viewed ovaries as a source of problems and needed to be removed.⁵⁴¹ {EL =
21 3]

22

23 Women and clinicians considering a prophylactic oophorectomy at the time of
24 hysterectomy should consider the use of other treatments, continued
25 monitoring and/or diagnostic imaging. An evaluation of the costs and benefits

of a national screening programme for ovarian cancer is currently underway in the UK.

13.4 Evidence statement on oophorectomy

Evidence from observational studies highlighted that the reasons for undertaking prophylactic oophorectomy for ovarian cancer, at the time of hysterectomy, were related to perceived risk of endometrial cancer.

13.5 GDG interpretation of evidence on oophorectomy

The GDG placed a high value on women retaining their ovaries.

The GDG discussion focused on the following issues:

- Undertaking oophorectomy after hysterectomy can present technical problems for the surgeon.
- Not undertaking oophorectomy at time of hysterectomy can lead to increased long-term problems, such as cancer.
- Age needs to be taken into account, not only as a marker for cancer risk, but due to QoL issues, such as long-term HRT use and loss of fertility.
- Likelihood of residual ovary syndrome occurring has to be considered as an indication for oophorectomy.

13.6 Recommendations on oophorectomy

A full discussion before ovaries are to be removed of the impact on HRT use and other effects should take place. **[D(GPP)]**

1

2 Women should be informed of the risk of premature loss of ovarian function
3 even when they are retained. **[D(GPP)]**

4

5 Women should be informed about the impact of bilateral oophorectomy on risk
6 of ovarian cancer, breast cancer and uterine pathology. **[D(GPP)]**

7

8 Oophorectomy should not be undertaken with hysterectomy for HMB, without
9 full counselling and consent. **[D(GPP)]**

10

11 Women found to have a family history of ovarian cancer should be referred for
12 genetic counselling. **[D(GPP)]**

13

14 In women aged under 45 years considering hysterectomy for HMB and have
15 other symptoms that may be related to ovarian dysfunction then a trial of
16 medical ovarian suppression for 3 months should be used as a guide to the
17 need for oophorectomy. **[D(GPP)]**

18

19

14 Competencies

Many of the interventions and diagnostic tools examined in this guideline require a high degree of operator competence. In this section, the minimum training and education requirements for an operator to be considered competent to undertake the following procedures are outlined: ultrasound; fit an LNG-IUS; endometrial ablation; myomectomy; UAE; hysterectomy with or without oophorectomy. In addition, the level of activity an operator needs to undertake to maintain competence and the audit standards required to monitor this activity are assessed. The framework used for assessment of competencies is outlined in appendix B.

14.2 Review on competencies

Limited data was identified from literature searches on issues relating to competencies. The available evidence for specific interventions is outlined below:

Ultrasound

No references were found for this procedure.

LNG-IUS

No references were found for this procedure.

Endometrial ablation

1 One audit study on endometrial ablation found that of 5388 TCREs
 2 undertaken, 1095 were by surgeons who had not attended a training course
 3 and who were not supervised. The study also found that of 983 laser
 4 ablations undertaken, 15 were by surgeons who had not attended a training
 5 course and who were not supervised. The study did not assess the outcomes
 6 of surgery, so it is unknown what effect the lack of training or supervision had.

7 {24680} [EL = 3]

8

9 An audit undertaken in the UK examined 18641 endometrial ablations. The
 10 study found a statistical significant trend in rates of immediate complications
 11 assessed by operator volume ($p < 0.05$).⁵⁴² [EL = 3]

12

13 An audit undertaken in Scotland examined 978 endometrial ablations. The
 14 audit found no association between operator volume and complication or
 15 satisfaction rates. However, the audit was based on voluntary submission of
 16 results.⁵⁴³ [EL = 3]

17

18 *Myomectomy*

19 No references were found for this procedure.

20

21 *UAE*

22 One set of training standards for UAE determined that training fellows must
 23 undertake 100 arteriographic procedures, including at least 50 visceral
 24 catheterisations and 25 selective embolisation procedures per year.⁵⁴⁴ [EL =
 25 4]

26

One set of training standards for UAE determined that training fellows must undertake 50 to 150 diagnostic arteriograms, 65 to 130 angioplasties and an unspecified number of visceral embolisations.⁵⁴⁵ [EL = 4]

One article on volume-outcome relationships was identified. One consensus statement on UAE suggests that between 12.5 and 25 UAEs need to be undertaken per year to remain competent.⁵⁴⁶ [EL = 4]

Hysterectomy & oophorectomy

Four volume-outcome studies were identified relating to hysterectomy. Most of the studies found a volume outcome relationship for hysterectomy, but these studies did not account for case-mix or differentiate between surgeon and hospital volume, or the type of hysterectomy being undertaken.

One cohort study compared the relationship between patient outcome and volume of surgery undertaken by the surgeon for several interventions, including abdominal hysterectomy for any indication. The study found that the volume-outcome relationship for hysterectomy was non-significant.⁵⁴⁷ [EL = 2+]

One cohort study on women who had undergone LAVH for benign disorders found that complications were reduced after the surgeon had undertaken 30 procedures, and that this should be the number required to become competent.⁵⁴⁸ [EL = 2+]

1 One audit study (n = 20249) found that difference between expected and
 2 actual mortality rates for hysterectomy for any indication were related to
 3 volume of procedures performed (actual versus expected mortality by volume
 4 performed: 1 to 24 hysterectomies per year OR = 1.874; 361 or more
 5 hysterectomies per year OR = 0.733).⁵⁴⁹ [EL = 3]

6

7 One study (n = 6609) found that complications rates with hysterectomy for any
 8 indication were related to volume of procedures undertaken (OR comparing
 9 low to high volume by procedure: hysterectomy = 1.35 (95% CI 1 to 1.82)).⁵⁵⁰
 10 [EL = 3]

11

12 These results do not allow a specific figure for the minimum numbers of
 13 procedures to be performed to be outlined. What they do show is that a
 14 volume relationship is likely to exist, and therefore a policy towards higher
 15 rather than lower volume of surgery by surgeons and within hospitals should
 16 be encouraged.

17

18 **14.3 GDG discussion on competencies**

19

20 Given the limited amount of the evidence available on competencies, the
 21 GDG discussion was the basis for recommendations. In addition, meeting
 22 were held with experts and their views were included in the discussion. The
 23 GDG discussion highlighted the following issues:

- 24 ▪ The GDG highlighted the variability in training undertaken by clinicians.
 25 (The GDG defined a training programme as any form of formal
 26 education, such as apprenticeship or course attendance.) The GDG

1 felt that it is essential that any operator must have completed an
2 accredited training programme provided by a relevant professional
3 organisation before undertaking a procedure.

- 4 ■ Given the limited data available on volume-outcomes effects, the GDG
5 did not feel that they could make valid recommendations on a minimum
6 level of activity. However, they did feel that encouraging higher volume
7 was necessary, and that this may mean limiting the number of
8 practitioners undertaking a procedure.

- 9 ■ However, the GDG stated that any minimum level of activity would
10 have to take into account the patient case-mix and the generic nature
11 of procedures, such as the ability to close wound.

- 12 ■ The GDG felt that there is a need for a service framework to be in place
13 for maintaining competencies and audit standards. This was seen as
14 being of significant importance. Once a framework was in place then
15 standards outlined in guidelines could be implemented in a systematic
16 manner. If frameworks do not exist then introduction of standards is
17 more difficult.

- 18 ■ Any system should include a mechanism for the reporting of any
19 complications to an operator and for the regular forum for discussion of
20 cases amongst colleagues.

- 21 ■ The GDG felt that information on operator competence should be
22 available to any prospective patient. This information could include
23 training completed, number of procedures undertaken and their
24 complications rates. However, the GDG recognised that providing raw

1 figures without explanation could be create confusion for women about
2 what they meant.

- 3 ▪ Given that the range of treatments available is increasing and the
4 number of women being treated is often stable or falling, it was felt that
5 there was a need for sub-speciality training and accreditation. For
6 example, not all trainees may need to be trained in hysterectomy for
7 HMB as not all will be required to undertake this procedure.
- 8 ▪ A system needs to be in place for MHRA Device Alerts to be
9 incorporated into training programmes
- 10 ▪ One option that the GDG believed would be helpful was that referral for
11 a procedure should be to a specific operator with special
12 interest/training in the area. This will ensure that any potential volume-
13 outcome effect is maximised and clinical governance ensured.
- 14 ▪ Given the range of endometrial ablation techniques available, it is
15 essential that any individual undertakes education and training in each
16 technique in order to gain proficiency in each.
- 17 ▪ The GDG also felt that where possible, ultrasound should be
18 undertaken in a dedicated gynaecological ultrasound unit, as the
19 specialist knowledge in such a unit provided better results.
- 20 ▪ Diagnostic Laparoscopy will be part of Core Training but all types of
21 hysterectomy will be taught as part of Special Skills Modules i.e. not all
22 trainees will learn these skills.
- 23 ▪ Hysterectomy for fibroids should be done in specialist centres with
24 experience in advanced open surgery.

- The number of cases will also depend on the overall profile of cases of a particular surgeon.
- Other appropriate specialists should be available.

14.4 Evidence statement for competencies

The results of GDG discussion highlighted a series of generic issues relating to education and training, and maintenance of skills for any procedure. There is a need for accredited training being completed prior to a procedure being undertaken. Referral should be made to those clinicians with specialist training and experience in a particular procedure. These clinicians should preferably be within specialist centres that have been accredited by a central body. Audit standards should be monitored centrally to ensure complete and transparent assessment of outcome. The GDG did not feel that making specific recommendations on activity levels without evidence of impact would be beneficial.

14.5 Recommendations for competencies

Training

On appointment to a consultant post, clinicians should demonstrate completion of an accredited training programme in an established procedure and this will be assessed on acquisition of competence, prior to undertaking that procedure. **[D (GPP)]**

1 Operative competence of clinician trainees undertaking procedures to
 2 diagnose and treat HMB should be formally assessed by trainers through a
 3 structured process such as that defined within training schemes of the Post-
 4 graduate Medical Education & Training Board and/or Royal Colleges. **[D**
 5 **(GPP)]**

6
 7 Training programmes must be available of sufficient length to allow clinicians
 8 time to achieve competency in complex procedures (e.g. operations for large
 9 fibroids or when sited in an awkward position) when these are appropriate.
 10 These will usually be sited in units with a particular interest and sufficient
 11 workload to facilitate this. **[D (GPP)]**

12
 13
 14 *Maintain*

15 Maintenance of surgical or radiological skills requires a robust clinical
 16 governance framework, this will include audit of numbers, case-mix, outcomes
 17 of all treatments both at the individual operator and organisational level.
 18 These data should be used to demonstrate good clinical practice. **[D (GPP)]**

19
 20 Established clinicians should be able to demonstrate that their training,
 21 experience and current practice at least equates to the standards laid out for
 22 newly trained clinicians. **[D (GPP)]**

23
 24 *Governance*

25 If a clinician lacks competence to undertake a procedure then they should
 26 refer to a clinician with the appropriate skill. Organisations should be

1 responsible through service specification based on robust audit data that
2 identify clinicians with the appropriate skills. **[D(GPP)]**

3

4 **14.6 Research recommendation**

5 Volume-outcome relationships in gynaecological procedures taking into
6 account patient case-mix, hospital and operator factors.

1 **Appendix A Health Economics**

2 As part of the guideline development process a health economics component
3 was included in each of the guideline questions. A systematic review of the
4 literature was undertaken to identify relevant economic evidence for each
5 question. Where evidence that met the inclusion criteria was identified, it was
6 summarised in the appropriate section of the guideline. Where suitable
7 evidence was identified no modelling was conducted to addresses, these
8 questions. The areas where evidence was identified were: information
9 provision, LNG-IUS, Endometrial Ablation, UAE and hysterectomy.

10

11 The GDG, with the guidance of the health economist, identified two areas of
12 the guideline pathway where it was felt health economic evidence was lacking
13 and that further analysis through decision modelling was required. The two
14 areas were investigations for HMB and pharmaceutical treatment for HMB.
15 Decision-analytic models were developed to address these questions and the
16 results are presented in this section. Where the answers to these questions
17 inform particular clinical questions, a summary of results has also been
18 presented in the appropriate section of the guideline.

19

20 The first question presented in this section is the cost-effectiveness of medical
21 treatments for menorrhagia in primary care. A number of articles related to
22 the cost-effectiveness of the LNG-IUS when compared with hysterectomy
23 were identified. These are summarised in the appropriate section of the
24 guideline.

1

2 The second question that is considered is the cost-effectiveness of imaging
3 techniques for the diagnosis of intra-uterine pathologies on referral to
4 secondary care.

5

1 **A cost-effectiveness analysis of first-line medical**

2 **treatments for uncomplicated HMB**

3 **Methods**

4 This model addresses the cost-effectiveness of four drugs commonly used to
 5 treat HMB. No economic evidence comparing the effectiveness of the
 6 selected treatments was found, and the GDG considered the development of
 7 an economic model a priority, given the common nature of the problem, the
 8 high decrement to quality of life for women with the problem, and the variety of
 9 treatments commonly used. An economic model allows for the evaluation of
 10 different treatment strategies in order to compare their relative costs and
 11 benefits.

12
 13 A state-transition (Markov) model is used to assess the cost-effectiveness of
 14 the four medical treatments. Markov models used in decision analysis are
 15 comprised of a series of cycles of equal length. A hypothetical cohort of
 16 patients in the model, spend each cycle in the model in a particular health
 17 state (e.g. good health, poor health, death). Patients can move between
 18 health states with given probabilities estimated from clinical data on the
 19 effectiveness of treatment. Each health state accrues both costs (of
 20 treatment) and health benefits associated with being in that state (measured
 21 in quality adjusted life years). This approach is useful because it allows the
 22 comparison of the costs and effects of alternative treatments for illnesses
 23 where disease states recur over time. This approach is therefore appropriate
 24 for HMB given the long-term nature of the condition, the very high likelihood of

recurrence if treatment is stopped, and the potentially high rates of discontinuation for some medical treatments. The health states used in this menorrhagia model are described below (Table A.1). A five year time horizon was chosen as this is the maximum time for which one of the treatments considered is licensed. A three-month cycle length was selected based on the available evidence, the expert opinion of the GDG and current practice for the medical management of HMB. In total, the model runs for 20 cycles (4 cycles per year).

The four treatments compared in the model are:

- Combined oral contraceptive pill (COCP)
- Tranexamic acid
- Levonorgestrel-releasing intrauterine system (LNG-IUS)
- Non-steroidal anti-inflammatory drugs (NSAIDs; mefenamic acid).

Three distinct analyses are undertaken using the Markov model:

All medical treatments are compared with watchful waiting

Hormonal treatments only are compared with surgical treatment, and

Non-hormonal treatments only are compared with watchful waiting

All medical treatments versus watchful waiting

None of the four treatments can be considered the primary medical treatment for HMB, as all four are widely used. In order to make appropriate comparisons, the treatments must be assessed against a relevant alternative baseline treatment. The initial baseline treatment for comparison in this model is watchful waiting, or no medical treatment. This has been selected as the

1 comparator for three reasons: the condition is not life threatening, and so it is
2 a viable management option; there is no primary medical therapy – a number
3 of different treatments are presently licensed and prescribed for this condition;
4 and, as per the evidence presented in the guideline, there are no indications
5 for direct referral for surgery as a first line treatment where uncomplicated
6 menorrhagia is suspected (uncomplicated meaning: pathology not identified or
7 is not sufficient to require specialist treatment).

8

9 *Hormonal treatments versus surgical intervention*

10 Although surgical interventions for uncomplicated menorrhagia (hysterectomy
11 and endometrial ablation) are not considered as a comparator in the overall
12 analysis, they play an important role in the management of this condition. In
13 women who have completed their families and who do not wish to retain their
14 fertility, surgical treatment may be an appropriate intervention. For this
15 reason, a separate analysis is undertaken of those medical treatments that
16 provide contraceptive benefits in comparison to a direct referral to surgery.

17

18 *Non-hormonal treatments versus watchful waiting*

19 Some women may wish to retain their fertility, and a further analysis is
20 undertaken only of those treatments that do not provide contraception
21 (tranexamic acid and NSAIDs). These are compared with a strategy of no
22 treatment, as surgical treatment for uncomplicated menorrhagia does not
23 allow a woman to retain her fertility (except for use of myomectomy for
24 treatment of uterine fibroids).

25

1 *Structure of the model*

2 At the beginning of each model cycle, a patient may be in one of seven
 3 specified health states. A person can only be in one health state during one
 4 cycle. Patients only move between states at the end of each cycle. All health
 5 states and probabilities used in the model are outlined in Table A.1. A
 6 diagram* showing the possible health states and all the plausible transitions
 7 between health states is presented in Figure A.1.

8 **Table A.1:** Markov model health states

State	Description and possible state transitions
Not well	All patients spend the first cycle of the model in the 'Not well' state. A patient in this state has perceived heavy bleeding. From this state, a patient can move to the 'Well' state if the heavy bleeding is resolved after treatment. If the bleeding is not resolved, they move to the 'Recurrence - Discontinue treatment' state. Patients cannot enter this state following the initial cycle - if a patient is not well following the initial treatment cycle, they are defined as having a recurrence and move to the appropriate cycle described below.
Well	A patient can only enter this state following successful medical treatment in the initial cycle. A patient in this state has no perceived heavy bleeding. It is assumed that a medical treatment that is effective following the initial treatment cycle will continue to be effective. Patients who choose to discontinue treatment when in the Well state are assumed to do so for reasons unrelated to the efficacy of the treatment, such as unpleasant side effects. Following a period spent in the 'Well' state, a patient may continue in this state or, for

* An influence diagram is a visual representation of a decision process.

	the reasons outlined, move to the 'Recurrence - Discontinue treatment' state.
Recurrence - Discontinue treatment	Patients that have chosen to discontinue treatment will spend a cycle in this state. A majority of women will have surgical treatment following the discontinuation of medical treatment, although some will choose to receive no further treatment. From this state, a patient will enter either the 'Surgery' state or the Recurrence - No further treatment' state.
Recurrence - No further treatment	A patient that enters this state will continue in this state until the end of the model period.
Surgery	Patients that discontinue medical therapy will generally have some form of surgical intervention. Following a period spent in this state, patients move to the 'Well' following surgery state.
Well following surgery	A patient will enter this state following successful surgical treatment. They will remain in this state until the final model cycle.
Dead	Following any cycle in the model, a patient has a certain likelihood of moving to the 'Dead' state. The likelihood of moving to this state is based on the natural rate of death of the patient population, as established by the life-tables for England. Patients that undergo surgical treatment also have an associated risk of death - this probability is taken from the relevant literature. Once a patient enters the 'Dead' state, they no longer accrue any costs or benefits.

- 1
- 2 Patients are assumed to enter the model at 35 years of age*. It is recognised
- 3 that in practice patients undergoing an initial medical treatment are likely to be

* The age at which patients enter the model can be adjusted to whatever age the GDG feel is appropriate. The importance of age lies in establishing the appropriate rate of death from other causes and has no bearing on the effectiveness of medical treatments.

1 younger on average than those who are referred for surgery, however there is
2 no evidence that age has any impact on the effectiveness of medical
3 treatments. The model considers a hypothetical cohort of 1000 patients
4 receiving each treatment option.

5
6 Initially the model only allows for one medical treatment to be used before a
7 patient is referred for surgical treatment, as no evidence was identified
8 assessing the effectiveness of one or more subsequent treatments when the
9 initial treatment has failed. A separate sensitivity analysis has been
10 undertaken to estimate in what proportion of women where the initial medical
11 treatment has failed a second medical treatment would be cost-effective.

12 13 14 **Treatment effectiveness**

15 A systematic review of the clinical and economic evidence was conducted for
16 the medical treatment of HMB and is presented in Chapters 6 and 7.
17 Wherever possible the values used to populate the Markov model have been
18 taken from the studies included in that review. In those instances where data
19 was not available from the systematic review, estimates were taken from the
20 best available published evidence source. Where no published evidence was
21 available, the expert opinion of the GDG members was sought. The values
22 used to estimate the clinical effectiveness for each medical treatment are
23 shown in Table A.2.

24
25 The complaint of HMB is a subjective one. Many women feel they have HMB
26 yet have a monthly blood loss below the clinical cut-off point of 80ml per cycle.

1 ¹²⁸ These patients still seek treatment due to the impact of the condition on
2 their quality of life. It is appropriate then to consider the success of any
3 treatment for menorrhagia in terms of the patient's perception of its impact on
4 their usual blood loss, and not on the average reduction in blood loss following
5 treatment as measured in many studies. As such, the analysis presented
6 here considers treatment success in terms of the proportion of women that are
7 satisfied; therefore, it is assumed that patients who continue (or indicate that
8 they would continue) to use a treatment are satisfied.

9

10 Patients that continue to feel they have HMB following medical treatment are
11 considered to have had unsuccessful treatment. Evidence from the
12 systematic review suggests that most women that have failed medical
13 treatment will undergo surgical treatment in an effort to resolve their HMB.

14 ^{248;330} It is necessary to include the costs and effects of surgical treatment
15 within the Markov model to accurately reflect the cost of failed medical
16 treatment.

17

18 A cost-effectiveness analysis of surgical interventions for uncomplicated
19 menorrhagia has recently been conducted as part of the Health Technology
20 Assessment of Endometrial Ablation.³³⁹ Data on the costs and effectiveness
21 of surgical treatment have largely been taken from this analysis and adapted
22 where necessary. Evidence that does not come from this analysis is taken
23 from the systematic review of surgical interventions for HMB in Chapters 10
24 and 12, or from other sources of published evidence where this is missing
25 from the systematic review. The expert opinion of the GDG was sought where

1 no published evidence was found. Details of the clinical parameters included
 2 in the surgical treatment analysis are found in Table 3 Uterine artery
 3 embolisation is a relatively new treatment for women with fibroids, and is not
 4 included in this model as insufficient data on which to make comparisons was
 5 available.

6

7 The outcomes of treatment in the analysis, is expressed in terms of quality
 8 adjusted life years (QALY) gained for each treatment. Published evidence
 9 sources were used to identify the quality of life weightings associated with
 10 living with HMB for one year; these values are described in detail in Table 4.

11

12 The following example illustrates how QALYs are calculated in this model.
 13 Heavy menstrual bleeding is associated with a quality of life of 0.50 – that is,
 14 patients who suffer from this illness have reported that they feel a loss in
 15 terms of quality of life that is equivalent to half a year at full health.⁵⁵¹ During
 16 the initial three-month cycle of the model spent in the ‘Not well’ state, the
 17 patient accrues 0.125 QALYs (0.50 QALYs per year/4 cycles per year). If the
 18 treatment is successful, the patient moves to the ‘Well following medical
 19 treatment’ state. During each subsequent model cycle spent in this state, the
 20 patient accrues 0.82 QALYs per full year, or. 0.21 QALYs¹⁰⁶ The QALYs
 21 accrued in each cycle are then summed to give the total number of QALYs for
 22 that patient during the five-year period of the model. Like costs, QALYs are
 23 discounted at 3.5% per annum (0.078% per cycle) to reflect the greater value
 24 attached to health gains made in the present relative to those made in the
 25 future.

1

2 *Treatment effectiveness tables*3 **Table A.2:** Medical treatment effectiveness parameters

Assumption	Value	Range	Source
COC pill			
Treatment success rate (proportion of women satisfied following treatment with COC pill)	0.30	0.10 – 0.68	Taking high and low estimates for other therapies and using a Triangular distribution
Proportion of women that discontinue treatment following a successful cycle of treatment	0.026	-	LARC (10 percent of women discontinue the pill in one year)
Likelihood that a successful treatment continues to work	1.00	-	GDG opinion
Proportion of women that discontinue treatment when there is perceived heavy bleeding following treatment	1.00	-	GDG opinion
Proportion of women who have surgical treatment following failed medical treatment	0.75	-	GDG opinion
LNG-IUS			
Proportion of women with LNG-IUS in situ after 12 months	0.68	0.61 to 0.75	Hurskainen ¹⁰⁷
Proportion of women with LNG-IUS in situ after five years	0.48	0.43 to 0.53	Hurskainen ¹⁰⁶

Proportion of women that discontinue treatment following a successful cycle of treatment:			Calculated from figures in Hurskainen ¹⁰⁶
Year 1	0.096	0.108 to	
Years 2 - 5	0.022	0.085 to 0.019 to 0.024	
Likelihood that a successful treatment continues to work	1.00	-	GDG opinion
Proportion of women that discontinue treatment when there is perceived heavy bleeding following treatment	1.00	-	GDG opinion
Proportion of women who have surgical treatment following failed medical treatment	0.83	1.00	Hurskainen ¹⁰⁶
Insertion failure rate	0.017	-	Hurskainen ¹⁰⁶
Tranexamic Acid			
Treatment success rate (proportion of women satisfied with Tranexamic Acid at one year)	0.77	0.67 – 0.87	Bonnar and Sheppard, ³⁰⁷
Proportion of women that discontinue treatment following a successful cycle of treatment	0.046	-	Bonnar and Sheppard, ³⁰⁷
Likelihood that a successful treatment continues to work	1.00	-	GDG opinion
Proportion of women that discontinue treatment when	1.00	-	GDG opinion

there is perceived heavy bleeding following treatment			
Proportion of women who have surgical treatment following failed medical treatment	0.75	-	GDG opinion
NSAIDs (Mefenamic acid)			
Treatment success rate (proportion of women satisfied with NSAIDs at one year)	0.74	0.64 - 0.84	Bonnar and Sheppard, 307
Proportion of women that discontinue treatment following a successful cycle of treatment	0.064	-	Bonnar and Sheppard, 307
Likelihood that a successful treatment continues to work	1.00	-	GDG opinion
Proportion of women that discontinue treatment when there is perceived heavy bleeding following treatment	1.00	-	GDG opinion

1

2 **Table A.3:** Surgical treatment effectiveness parameters

Parameter	Value	Range	Source
Initial surgical treatment			
Proportion of women who have surgical treatment following failed medical treatment	0.75	-	GDG opinion

Proportion of women who undergo hysterectomy as surgical treatment for menorrhagia	0.43	-	Reid (In press)
Proportion of women who undergo TCRE as surgical treatment for menorrhagia	0.25	-	Reid (In press)
Proportion of women who undergo MEA as surgical treatment for menorrhagia	0.16	-	Reid (In press)
Proportion of women who undergo TBEA as surgical treatment for menorrhagia	0.16	-	Reid (In press)
Prevalence of fibroids	0.30	-	Vercellini [in Farquhar ¹⁵⁴]
Proportion of women with fibroids that have surgery (hysterectomy or myomectomy)	0.85	-	GDG opinion
Complications after hysterectomy	0.086	-	Maresh ⁵²¹
Death after hysterectomy (direct cause)	0.00038	-	Maresh ⁵²¹
Average waiting time for hysterectomy	83 days	-	HES Data
Average waiting time for ablation	94 days	-	HES Data
Recurrence following ablation			
Recurrence of menorrhagia following ablation (all methods)	0.10	-	Garside review of evidence ³³⁹
Proportion with failed first ablation (all methods) having	1.00	-	Assumption in Garside ³³⁹

further treatment			
Proportion of women having further treatment that have hysterectomy	0.60	-	Cooper ⁵⁵²
Proportion of women having further treatment that is repeat ablation	0.40	-	Garside review of evidence ³³⁹
Recurrence of menorrhagia following second ablation	0.10	-	Garside review of evidence ³³⁹
Proportion of women with failed second ablation (all methods) having hysterectomy	0.90	-	Professional estimate assumed in Garside ³³⁹

1

2 **Table A.4:** Quality of life values

Health state	Value per year (95% C.I.)	Value per cycle (range based on 95% C.I.)	Source
Unwell (perceived heavy bleeding)	0.50 (0.48 to 0.52)	0.125 (0.12 to 0.13)	Sculpher ⁵⁵¹
Well following medical treatment (no perceived heavy bleeding)	0.84 (0.73 to 0.93)	0.21 (0.183 to 0.233)	Hurskainen ¹⁰⁶
Well following surgical treatment (no perceived heavy bleeding)	0.88 (0.75 to 0.95)	0.22 (0.188 to 0.238)	Hurskainen ¹⁰⁶

Complications following surgery	0.50 (0.48 to 0.52)	0.125 (0.12 to 0.13)	Sculpher ⁵⁵¹
Quality of life scores for a reduction in heavy bleeding are estimated to be the same for all medical treatments – it is assumed that the quality of life refers to the state of no heavy bleeding following medical treatment, rather than for the effect of a particular drug. The side effect profile of each drug may have an effect on the resulting quality of life scores, though there is no evidence of this; impacts of side effects are assumed to be captured in the discontinuation rate for each drug.			
Quality of life scores for surgery are assumed as the score for hysterectomy, as hysterectomy is the most common surgical procedure undertaken for HMB. While it is likely that the difference in QALYs gained will be reduced as more non-hysterectomy procedures are undertaken, the difference in quality of life for second generation ablation techniques and hysterectomy is negligible.			

1

2

3 *Treatment Costs*

4 This analysis assumes an NHS perspective for the estimation of costs, as
5 required by NICE guidance. Costs include the medical management of
6 menorrhagia in a primary care setting, and surgical treatment in a secondary
7 care setting. In line with NICE recommendations, this analysis does not
8 consider costs to the patient associated with the condition or its treatment
9 (such as time off work or transportation to and from appointments). All costs
10 are discounted at 3.5% per annum as recommended by NICE.

11

12 The costs of medical treatments for HMB are comprised of the cost of
13 individual medicines and devices, the costs associated with the initial GP
14 consultation, the fitting of devices where appropriate, routine follow-up
15 consultations and a consultation if a decision is taken to discontinue

1 treatment. Costs associated with the management of side effects from
 2 medical treatment are not included in full, as there is insufficient evidence
 3 upon which to draw. However, the impact of side effects on quality of life is
 4 captured in part by the discontinuation rate of treatments.

5
 6 When medical treatment fails, many women will undergo surgical treatment.
 7 Patients referred for specialist care will require investigations to explore the
 8 cause of the HMB, followed in most cases by surgery. Investigations will
 9 involve consultation with a specialist and ultrasound exam to exclude any
 10 intrauterine pathology and to identify fibroids. Surgical treatment is dependent
 11 on the results of the imaging examination and subsequent diagnosis. The
 12 costs for surgical treatment, including diagnostic investigations, are detailed in
 13 Table A.6.

14
 15 The source for each element of the costs for both medical and surgical
 16 components of the model is included in Tables 5 and 6. Where possible, costs
 17 have been taken from published sources. The costs associated with imaging
 18 are taken from analysis conducted for guideline, where the cost-effectiveness
 19 of diagnostic imaging is considered. All costs have been adjusted in line with
 20 the Hospital and Community Health Service index to 2004 prices. Some costs
 21 are subject to uncertainty and this is addressed in the sensitivity analysis.

22
 23 **Table A.5:** Cost data for medical treatments used in the model

Parameter	Cost (£)	Range	Source
COC pill			

Initial GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Three month follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Routine annual follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Cost per model cycle of COC pill (levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms)*	8.31	7.44 - 9.18	BNF 50 (September 2005)
Initial stage cost	56.31	55.44 - 57.18	Includes cost of initial GP consultation, three month follow-up consultation and cost of treatment
Incremental stage cost	14.31	13.44 - 15.18	Includes cost of drug and ¼ cost of follow-up appointment
Cost of discontinuation	24.00	-	Includes the cost of a GP consultation
*This particular combination was chosen because RCT evidence is available for its effectiveness in treating menorrhagia. Sensitivity analysis on this cost reflects the cost of different options for this formulation.			
LNG-IUS	Cost (£)	Range	Source
Cost of device	83.16	-	BNF (September 2005)
Initial consultation and fitting: GP (30 min) Practice Nurse (10 min)	72.00 4.30	-	Costs: PSSRU Unit costs of health and social care (2005) Length: GDG

			opinion/LARC
Sterile pack for insertion	18.20	-	Long-acting reversible contraception guideline (NICE)
4 – 6 week follow-up consultation: GP (10 min) Practice Nurse (10 min)	24.00 4.30	-	Costs: PSSRU Unit costs of health and social care (2005) Length: GDG opinion/LARC
Three month follow-up consultation: GP (10 min)	24.00	-	Costs: PSSRU Unit costs of health and social care (2005) Length: GDG opinion/LARC
Consultation for removal: GP (10 min) Practice Nurse (10 min)	24.00 4.30	-	Costs: PSSRU Unit costs of health and social care (2005) Length: GDG opinion/LARC
Routine annual follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Sterile pack for removal	3.17	-	Long-acting reversible contraception guideline (NICE)
Initial stage cost	229.66	206.69 - 252.63	Includes cost of initial GP consultation, three month follow-up consultation and cost of treatment
Incremental stage cost	6.00	-	Includes ¼ cost of annual follow-up appointment
Cost of discontinuation	31.47	-	Includes the cost of a GP consultation for removal

			and sterile removal pack
Tranexamic Acid	Cost (£)	Range	Source
Initial GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Three month follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Cost per model cycle of Tranexamic acid (based on 28 pills per cycle)	20.16	17.28 - 23.04	BNF 50. Base case reflects median drug cost.
Routine annual follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Initial stage cost	68.16	65.28 - 71.04	Includes cost of initial GP consultation, three month follow-up consultation and cost of treatment
Incremental stage cost	26.16	23.28 - 29.04	Includes cost of drug and ¼ cost of follow-up appointment
Cost of discontinuation	24.00		Includes the cost of a GP consultation
NSAIDs	Cost (£)	Range	Source
Initial GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Three month follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Cost per model cycle of	4.74	-	BNF 50

mefenamic acid (based on 45 pills per model cycle) – 500mg, 21 tablet pack = £2.21			
Routine annual follow-up GP consultation (10 minutes)	24.00	-	PSSRU Unit costs of health and social care (2005)
Initial stage cost	52.74	47.47 - 58.01	Includes cost of initial GP consultation, three month follow-up consultation and cost of treatment
Incremental stage cost	10.74	9.67 - 11.81	Includes cost of drug and ¼ cost of follow-up appointment
Cost of discontinuation	24.00	-	Includes the cost of a GP consultation

1

2 **Table A.6:** Costs of surgical treatment

Parameter	Cost per unit (£)	Range	Source
Initial consultation (20 min)	27.66	-	PSSRU Unit costs of health and social care (2005)
Second consultation (20 min)	27.66	-	PSSRU Unit costs of health and social care (2005)
Pre-operative clinic with nurse (20 min)	10.00	-	PSSRU Unit costs of health and social care (2005)
Full blood count	3.06	-	Royal Free Hospital
Transvaginal ultrasound	107.49	-	Critchley ⁷¹ and guideline analysis of imaging

			techniques.
Cost per surgery (hysterectomy or myomectomy)	2762.88	-	Lumsden (unpublished data)
Cost per trans-cervical resection of the uterus	1324.53	-	Garside ³³⁹
Cost per microwave endometrial ablation treatment	1123.22	-	Garside ³³⁹
Cost per thermal balloon endometrial ablation treatment	985.90	-	Garside ³³⁹

1

1

2 **Results**

3 The results of the economic analysis are presented in the form of incremental
4 cost-effectiveness ratios (ICERs), expressing 'additional cost per quality
5 adjusted life year gained' of one treatment compared with another. The
6 estimation of this ratio allows for a direct comparison between treatments,
7 assessing whether the additional benefit (quality adjusted life years) is worth
8 the additional cost when switching from one treatment to another. The
9 incremental cost-effectiveness ratios compare the relative cost-effectiveness
10 of different treatments for HMB, including watchful waiting, medical treatment,
11 and surgical treatment.

12

13 Treatments have been ranked from least to most costly with the baseline of no
14 treatment listed first where appropriate. Where one treatment is less costly
15 and provides greater benefit than another treatment, the first treatment is said
16 to dominate the alternatives. ICERs between the non-dominated methods
17 remaining in the analysis have been calculated.

18

19 The results of the analyses of the Markov model, for a cohort of 1000 women
20 with uncomplicated HMB, are presented in Tables 5, 6 and 7. Table 5 shows
21 the results when all treatments are compared to watchful waiting; Tables 6
22 compares hormonal treatments and surgical treatment; Table 7 compares
23 non-hormonal treatments with watchful waiting.

24

25 *All treatments versus watchful waiting*

Table A.7: Summary of the cost per QALY analysis for medical treatments at five years for a cohort of 1000 patients

Treatment	Total cost (£)	Incremental cost (£)	Total effect (QALYs)	Incremental effect (QALYs)	ICER (£/QALY)
No treatment	24,000	-	2444.82	-	-
LNG-IUS	1,177,910	1,153,910	3818.89	1374.07	840
Tranexamic acid	1,490,387	312,477	3751.07	-67.82	Dominated by LNG-IUS
NSAIDs (mefenamic acid)	1,529,051	351,141	3699.38	-119.50	Dominated by LNG-IUS
COCP	1,714,601	536,692	3610.71	-208.18	Dominated by LNG-IUS

All medical treatments are more costly and accrue a greater number of QALYs than no treatment. LNG-IUS accrues the greatest number of QALYs of all medical therapies compared and is less costly over five years than any of the other treatment options. The cost per additional QALY for choosing LNG-IUS in preference to no medical treatment is £840. Sensitivity analysis of this comparison showed that the relative cost-effectiveness of these treatments was not sensitive to changes in quality of life weights, treatment effectiveness parameters or costs and that the LNG-IUS as a first-line medical treatment is the only cost-effective strategy.

1 *Hormonal treatments versus surgery*

2 **Table A.8:** Summary of the cost per QALY analysis for hormonal medical
3 treatments at five years for a cohort of 1000 patients (hormonal treatments
4 compared to no treatment)

Treatment	Total cost (£)	Incremental cost (£)	Total effect (QALYs)	Incremental effect (QALYs)	ICER (£/QALY)
LNG-IUS	1,177,910	-	3818.89	-	-
Surgery	1,642,633	464,723	3596.81	-222.08	Dominate d by LNG-IUS
COC	1,714,601	536,692	3610.71	-208.18	Dominate d by LNG-IUS

5

6 The contraceptive medical treatments are compared only to surgical
7 treatments, as a loss of fertility is generally a consequence of surgical
8 treatments (apart from myomectomy for women with uterine fibroids).

9

10 The LNG-IUS is the least costly of the three options compared. Both direct
11 referral for surgery and the oral contraceptive pill, accrue fewer QALYs at a
12 greater cost than LNG-IUS. As reported in the systematic review of hormonal
13 treatments (Chapter 5), little clinical evidence of sufficiently high quality was
14 found that evaluated the combined oral contraceptive pill as a treatment for
15 menorrhagia, and therefore the results should be interpreted with caution.
16 However, sensitivity analysis showed that the results of this comparison were

not sensitive to changes in the rate of effectiveness for this treatment, and at all values considered, LNG-IUS is the only cost-effective strategy.

Non-hormonal treatments versus watchful waiting

Table A.9: Summary of cost-quality of life analysis for non-hormonal medical treatments at five years for a cohort of 1000 patients

Treatment	Total cost	Incremental cost	Total effect	Incremental effect	ICER
	(£)	(£)	(QALYs)	(QALYs)	(£/QALY)
No treatment	24,000	-	2444.82	-	-
Tranexamic acid	1,490,387	1,466,387	3751.07	1306.25	1,123
NSAIDs (mefenamic acid)	1,529,051	38,664	3699.38	-51.68	Dominated by tranexamic acid

When compared with a strategy of watchful waiting, both NSAIDs and tranexamic acid generate more QALYs but at a greater cost. The cost per additional QALY for choosing tranexamic acid over watchful waiting is £1,123. NSAIDs generate fewer QALYs at a greater cost than tranexamic acid. Sensitivity analysis showed that this result was not sensitive to changes in quality of life weights, treatment effectiveness rates or costs; at all values considered, tranexamic acid is the cost-effective option.

1 The cost-effectiveness of using more than one

2 medical treatment before referral to surgery

3

4 The use of a second or third medical treatment in the event of an initial
5 medical treatment failing is an important part of clinical practice. However, no
6 evidence assessing the effectiveness of multiple medical treatments was
7 identified in the literature review. In the absence of this evidence, it would be
8 unreasonable to assume that the treatment effect of subsequent treatments is
9 independent of the result of the initial treatment. To address this question, the
10 Markov model used in the previous analyses has been modified to estimate
11 the minimum treatment effect required for a second medical treatment to be
12 considered cost effective against strategies that involve only a single medical
13 treatment prior to referral for surgery.

14

15 Only those treatments that have been recommended as first-line medical
16 treatments in this guideline have been considered as first-line treatments in
17 this analysis. Two strategies assuming there was no preference for
18 contraceptive benefit were assessed, one strategy was assessed where it was
19 assumed that contraceptive benefit was sought, and one strategy was
20 considered for those women wishing to avoid contraceptive benefits. The four
21 additional strategies considered were:

- 22 ▪ LNG-IUS followed by the COC pill
- 23 ▪ LNG-IUS followed by tranexamic acid
- 24 ▪ LNG-IUS followed by mefenamic acid

- 1 ▪ Tranexamic acid followed by mefenamic acid

2 A key assumption in this analysis is that a subsequent medical treatment is
 3 only considered where the first treatment has failed in the initial model cycle.
 4 Strategies involving two medical treatments are not compared with one
 5 another, as there is no accepted level of effectiveness for any treatment, and
 6 thus no basis for comparison.

8 **Results**

9 For each two-treatment strategy, there is a level of clinical effectiveness
 10 where the strategy is more effective and less costly than a single treatment
 11 strategy. Where this is the case, the strategy should be adopted if it is
 12 believed that the treatment is likely to be effective in that proportion of
 13 patients. If that is not the case, the treatment should only be adopted if the
 14 expected level of effectiveness generates a cost saving of greater than
 15 £20,000 per QALY. The strategy requiring the lowest level of clinical
 16 effectiveness for the second medical treatment in order to be considered cost-
 17 effective is that of LNG-IUS followed by tranexamic acid. This strategy should
 18 considered cost-effective if tranexamic acid is effective in at least 13% of
 19 patients where LNG-IUS has failed. At this level of effectiveness, the strategy
 20 is cost saving - it generates fewer QALYs but at a lower cost.

21
 22 The level of clinical effectiveness for each strategy where it costs less and
 23 generates a greater number of QALYs is:

- 24 ▪ 0.25 for LNG-IUS followed by tranexamic acid when compared with LNG-
 25 IUS alone,

- 1 ▪ 0.28 for LNG-IUS followed by COC pill when compared with LNG-IUS
- 2 alone,
- 3 ▪ 0.33 for LNG-IUS followed by NSAIDs when compared with LNG-IUS
- 4 alone, and
- 5 ▪ 0.38 for tranexamic acid followed by NSAIDs when compared with
- 6 tranexamic acid alone.

7 ▪

8 For a strategies-considered cost saving, at a threshold willingness to pay

9 value of £20,000 per QALY then:

- 10 ▪ LNG-IUS followed by tranexamic acid is cost-effective when the additional
- 11 treatment is effective in approximately 13% of the remaining patients.
- 12 ▪ LNG-IUS followed by the combined oral contraceptive pill is cost-effective
- 13 when the additional treatment is effective in 15% or more of remaining
- 14 patients.
- 15 ▪ LNG-IUS followed by NSAIDs is cost-effective when the additional
- 16 treatment is effective in approximately 15% of remaining patients.
- 17 ▪ Tranexamic acid followed by NSAIDs is cost effective when the additional
- 18 treatment is effective in approximately 20% of remaining patients.

19

The cost-effectiveness of imaging for the exclusion of structural abnormalities of the uterus in women with uncomplicated menorrhagia

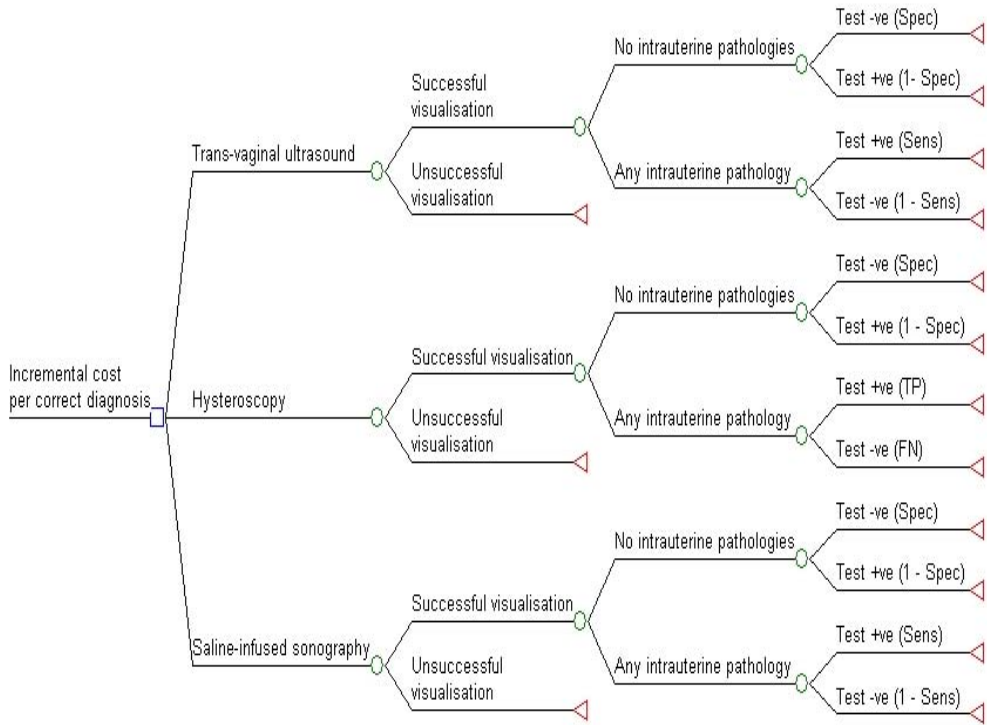
Methods

When patients feel that medical treatment has not successfully resolved their bleeding, they will often be referred to secondary care by their GP. Following consultation with a specialist and prior to any surgical treatment, most patients will undergo an imaging examination to confirm or deny the presence of certain pathologies such as fibroids or polyps that may be responsible for the bleeding. The imaging techniques most commonly used in the NHS for this procedure are transvaginal ultrasound and hysteroscopy. Saline-infused sonography is a third alternative that, while used in other countries, is not widely available at present within the NHS. The model examines the cost-effectiveness of these three imaging methods, expressed in terms of cost per correct diagnosis.

A decision analytic model was developed using TreeAge Pro 2005 (Figure A.2), specialised decision analysis software. Prior to visualization, patients in the model were assumed to have one of two health states: no intrauterine pathology, or any intrauterine pathology. Following the examination, patients will be given a true positive or negative diagnosis, or a false positive or negative diagnosis. The model does not follow patients beyond an initial

1 diagnosis, as the range of potential pathologies and treatments is beyond the
2 scope of the guideline.

3 **Figure A.2:** Cost-effectiveness of imaging for intrauterine pathology decision
4 tree



5
6 It will not be possible to conduct a successful visualization in all patients.
7 Where visualization is unsuccessful, patients drop out of the pathway and do
8 not re-enter the model, as evidence was not found to estimate the likelihood of
9 success for a second attempt at visualisation using the techniques under
10 consideration. In the absence of specific evidence, independence between the
11 first result and second result cannot be assumed. Full test costs are still
12 incurred for all unsuccessful visualisations.

13

14 *Clinical effectiveness*

1 Estimates of the diagnostic accuracy of each imaging method are taken from
 2 a systematic review ¹⁵⁴ of investigations for abnormal uterine bleeding in pre-
 3 menopausal women. The original source of each estimate is indicated in
 4 Table A.10 and these estimates are taken from this review. Individual studies
 5 included in the review were not retrieved. Estimates of the number of
 6 successful visualisations are taken from a health technology assessment
 7 examining outpatient procedures for the investigation of women with abnormal
 8 uterine bleeding. ⁷¹

10 **Table A.10:** Diagnostic test effectiveness and range for sensitivity analysis ⁷¹

Diagnostic test	Value (Source)	Range (Source)
Trans-vaginal sonography		
Sensitivity (%)	96 (Vercellini, 1996)	48 to 100 (Krampl, 2001; Fedele, 1991)
Specificity (%)	86 (Vercellini, 1996)	28 to 100 (Bronz, 1997; Fedele, 1991)
Successful visualisations (%)	88 (Critchley ⁷¹ , 2001)	79 to 97 (+/- 10%)
Saline-infused sonography		
Sensitivity (%)	87 (Schwarzler, 1998)	87 to 100 (Schwarzler, 1998; Dijkhuizen, 1999)
Specificity (%)	91 (Schwarzler, 1998)	50 to 100 (Ossola, 1999; Gronlund, 1999)

Successful visualisations (%)	83 ^{xx}	Minimum range of hysteroscopy to maximum range TVS
Hysteroscopy		
Sensitivity (%)	90 (Schwarzler, 1998)	90 to 97 (Schwarzler, 1998; Widrich, 1996)
Specificity (%)	91 (Schwarzler, 1998)	62 to 93 Ossola, 1999; Widrich, 1996)
Successful visualisations (%)	77 (Critchley ⁷¹ , 2001)	70 to 85 (+/- 10%)
Prevalence of uterine pathology		
A priori probability of any intrauterine pathology (%)	61 (Vercellini, 1997)	-

1

2

3 *Costs*

4 Costs are estimated at 2004 prices, with costs from earlier years being
5 adjusted according to the Hospital and Community Health Services pay and
6 prices index. The perspective adopted for the economic evaluation is that of
7 the NHS, in line with NICE guidance on economic evaluations for guidelines.

8 Costs included in the model are comprised of the staff and equipment costs
9 necessary to carry out the described examinations. Although the guideline
10 does not address service configuration, assumptions are made in the model
11 about the setting in which each procedure is undertaken. The model does not
12 consider the future management of patients following examination. Due to the

^{xx} The rate of successful visualizations for saline-infused sonography was not identified in the review of the literature and has been estimated. This assumption is tested in the sensitivity analysis.

1 range of intrauterine pathologies requiring varied treatment regimes, the
 2 majority of which fall outside the scope of this guideline, it is not possible in
 3 this analysis to conduct a cost-effectiveness analysis of the diagnostic
 4 methods under consideration using quality adjusted life years as the outcome.

5 **Table A.11:** Cost of imaging procedures

	Cost per unit (£)	Range (£)	Source
Transvaginal ultrasound			
Gynaecological outpatient appointment	61.56	-	Critchley ⁷¹
Outpatient ultrasound session	45.93	-	Critchley ⁷¹
Total cost of transvaginal ultrasound (per procedure)	107.49	96.74 to 118.24	Range is +/- 10% of total cost
Saline infused sonography			
Gynaecological outpatient appointment	61.56	-	Critchley ⁷¹
Outpatient ultrasound session	45.93	-	Critchley ⁷¹
Consumables	37.62	0.00 to 100.23	Cost of TVS plus 35%; Dijkhuizen ⁵⁵³
Total cost of saline infusion sonography (per procedure)	145.11	107.49 to 209.72	Range is based on maximum and minimum costs of TVS and hysteroscopy
Hysteroscopy			
Gynaecological outpatient appointment	61.56	-	Critchley ⁷¹
Outpatient hysteroscopy (with reusable sheath)	148.16	-	Critchley ⁷¹
Total cost of hysteroscopy	209.72	188.75 to	+/- 10% of total cost

(per procedure)		230.69	
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1

2 Saline-infusion sonography is uncommon in the NHS, and no studies
3 providing UK costs were identified. Costs for this procedure have been
4 estimated as for trans-vaginal ultrasound plus the additional costs associated
5 with the saline infusion process. One comparison of imaging methods ⁵⁵³
6 estimated that the additional costs of saline-infused sonography increased the
7 cost of transvaginal ultrasound by approximately 35%. In the absence of
8 published UK costs, the cost of saline infused sonography has been estimated
9 as for transvaginal ultrasound plus 35%. Sensitivity analysis on this cost has
10 been undertaken to test the validity of this assumption.

11

12 The analysis assumes that the hysteroscopy procedure takes place in an
13 outpatient setting with a reusable sheath. This is the least costly option,
14 though the cost of outpatient hysteroscopy is explored in the sensitivity
15 analysis to allow for variation in the cost of reusable versus disposable
16 hysteroscopy equipment. Inpatient hysteroscopy is not explicitly considered;
17 costs in an inpatient setting are greater though there is no evidence that
18 accuracy differs between settings.

19

20 **Results**

21 The results of the analysis for a hypothetical cohort of 1000 patients are
22 presented in Table 3. Results are presented in order of least to most costly,
23 as both transvaginal ultrasound and hysteroscopy are in routine use at
24 present and neither can be considered the standard method against which the

other techniques can be compared. In the analysis, both saline-infused sonography and hysteroscopy are dominated by transvaginal ultrasound; that is, transvaginal ultrasound is both less costly and more accurate than the other methods compared here.

The cost per correct diagnosis for transvaginal ultrasound is £132.63, for saline-infused sonography it is £197.42 and for hysteroscopy £301.32. Using transvaginal ultrasound results in 810 correct diagnoses (at a total cost of £107,490), compared with just 735 correct diagnoses with saline infused sonography (£145,100) and 696 correct diagnoses with hysteroscopy (£209,720). Incremental cost-effectiveness ratios are not calculated, as transvaginal ultrasound is less costly and more accurate than the other methods and should be recommend as the standard imaging method for excluding structural abnormalities in women with HMB.

Table A.12: Cost per correct diagnosis at first visualisation (for a cohort of 1000 patients)

Imaging method	Total cost (£)	Correct diagnoses	Incremental cost	Incremental effect	ICER	Cost per correct diagnosis (£)
Transvaginal ultrasound	107,490	810	-	-	-	132.63
Saline infused sonography	145,100	735	37,610	-75	Dominated by TVS	197.42

Hysteroscopy	209,720	696	102,230	-114	Dominate d by TVS	301.32
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1

2 **Sensitivity Analysis**

3 Many of the parameters in this model are subject to uncertainty and a number
4 of one-way and threshold sensitivity analyses were undertaken to test the
5 robustness of the model. The ranges of the cost and effectiveness
6 parameters included in the sensitivity analyses are listed in Table A.11 and
7 Table A.12.

8

9 *Costs*

10 The greatest degree of uncertainty in the model was centred around the cost
11 of saline-infused sonography. No published studies provided data on the cost
12 of saline infused sonography in an NHS setting, and the GDG were unable to
13 identify a source to estimate the cost of the procedure. A comparison of
14 transvaginal ultrasound with saline infused sonography in the Netherlands,
15 with costs estimated in US Dollars, found that saline-infused sonography was
16 35% more costly than TVS, and as such, the costs for saline-infused
17 sonography were estimated in a similar manner for the purposes of this
18 model.⁵⁵³

19

20 To test the validity of this assumption, the costs for saline-infused sonography
21 were varied across a range of figures. When the cost of is equal to that of
22 TVS, saline-infused sonography provides each correct diagnosis at a cost of
23 £146.24, still greater than that of TVS. In order for saline-infused sonography
24 to provide each correct diagnosis at the same cost as TVS, each saline-

1 infused sonography procedure must cost £97.48. Given the additional
 2 expense incurred with saline-infused sonography compared with TVS, this
 3 value is unrealistic. There is therefore no cost at which saline-infused
 4 sonography will be cost-effective compared with TVS.

5

6 Hysteroscopy was the most costly and least effective of the three imaging
 7 techniques under consideration. The assumptions in the initial analysis used
 8 the least costly method of performing a hysteroscopy, using a re-usable
 9 sheath in an outpatient setting. This method was more costly and less
 10 effective than trans-vaginal ultrasound, so methods with additional costs
 11 (using disposable sheaths or performing the procedure in an inpatient setting)
 12 are not considered. A threshold analysis of the model shows that in order for
 13 hysteroscopy to generate the same cost per correct diagnosis, the procedure
 14 must cost no more than £92.32.

15

16 *Effectiveness*

17 The greatest range of uncertainty in the model parameters is found in the
 18 diagnostic accuracy of each imaging test. A systematic review found a wide
 19 range in the reported sensitivity and specificity for each test. The figures used
 20 in the analysis are assumed to be the best available estimates and are drawn
 21 from this review based on the evidence grade and sample size of the
 22 individual studies as reported in the review. Given the wide range of
 23 published figures, a series of one-way and two-way sensitivity analyses has
 24 been conducted to test the impact of variation in these parameters on the
 25 results of the model.¹⁵⁴

1

2 Transvaginal ultrasound had the widest range of reported results for sensitivity
 3 (48% to 100%) and specificity (28% to 100%). Under one-way sensitivity
 4 analysis, when sensitivity is varied to the minimum and maximum reported
 5 values, the cost per correct diagnosis ranges from £194.44 to £129.20. When
 6 specificity is varied to the minimum and maximum reported values, the cost
 7 per correct diagnosis for transvaginal ultrasound ranges from £175.80 to
 8 £125.20. Under a two-way sensitivity analysis, when sensitivity and specificity
 9 are varied to the maximum reported values, the cost per correct diagnosis is
 10 £122.15 (880 correct diagnoses). When the sensitivity and specificity of
 11 transvaginal ultrasound are varied to their minimum reported values, the cost
 12 per correct diagnosis is of transvaginal ultrasound is £303.85 (354 correct
 13 diagnoses). Under these conditions, transvaginal sonography is more costly
 14 and less accurate than either saline-infused sonography or hysteroscopy,
 15 though the difference with hysteroscopy is small, and the model may not be
 16 sensitive enough to detect accurately such a difference.

17

18 The sensitivity of saline-infused sonography ranged from 87% to 100%. The
 19 lower estimate is that used in the initial analysis. Specificity ranged from 50%
 20 to 100%. When the sensitivity is varied to the maximum reported value, the
 21 cost per correct diagnosis is £181.19 (801 correct diagnoses). When the
 22 specificity is varied between the minimum and maximum reported values, the
 23 cost per correct diagnosis is £240.91 (602 correct diagnoses) and £189.89
 24 (764 correct diagnoses) respectively. Under a two-way sensitivity analysis,
 25 when both the sensitivity and specificity of saline-infused sonography are

1 varied to their minimum reported values, the cost per correct diagnosis is
2 £240.91 (602 correct diagnoses). Under these circumstances, saline-infused
3 sonography is less effective and more costly than transvaginal ultrasound.

4
5 When sensitivity and specificity of saline-infused sonography are varied to the
6 maximum reported values, the cost per correct diagnosis is £174.83 (830
7 correct diagnoses). Under these conditions, when compared with the initial
8 analysis of transvaginal ultrasound, saline-infused sonography generates an
9 additional 20 correct diagnoses at an incremental total cost of £37,620, giving
10 a cost per additional correct diagnosis of saline-infused sonography when
11 compared with transvaginal ultrasound results of £1927.25.

12
13 The reported sensitivity for hysteroscopy ranged from 90% (as used in the
14 initial analysis) to 97% and specificity ranged from 62% to 93%. Varying the
15 sensitivity to the maximum value, hysteroscopy generates 729 correct
16 diagnoses at a cost of £287.73 each. At the minimum reported value for the
17 specificity of hysteroscopy, it generates 609 correct diagnoses at a cost of
18 £344.42 per correct diagnosis and at the maximum reported specificity it
19 generates 702 correct diagnoses at a cost of £298.74 per correct diagnosis.
20 When the sensitivity and specificity are both varied to the maximum reported
21 values, hysteroscopy generates 735 correct diagnoses at a cost of £285.38
22 each. At no values of the reported sensitivity and specificity of hysteroscopy
23 is cost-effective when compared with the initial results of transvaginal
24 ultrasound.

Only one study was identified that estimated the proportion of successful visualisations using hysteroscopy and transvaginal ultrasound. No published studies were identified that estimated the proportion of successful visualisations using saline-infused sonography, and this value was estimated at mid-way between the values for the other two procedures. Sensitivity analyses using the ranges estimated in table 2 was undertaken to test this assumption. In only one instance were the results of the model sensitive to the changes in the proportion of successful visualisations. When the rate of successful visualisations for saline infused sonography is varied to the maximum value tested of 97% (Table 2), it generates 49 additional correct diagnoses at a an additional cost of £37,967 when compared with transvaginal ultrasound, with an incremental cost per additional correct diagnosis of £774.84.⁷¹

Limitations of analysis

The economic analysis of diagnostic imaging techniques was based on the best available evidence. However, there are limitations that may reduce the general applicability of the model in an NHS setting, and these should be considered when interpreting the results.

The accuracy of each of the procedures considered in the model are to a greater or lesser degree operator dependent. That is, obtaining a correct diagnosis can be dependent on the skills and experience of the individual undertaking the imaging as well as the individual who interprets the results. The model is unable to explicitly account for the competencies of the various

1 operators involved throughout each imaging process. Some element of
2 operator competency may be captured in the sensitivity analysis, through the
3 range of sensitivity and specificity values examined for each procedure. It is
4 not possible however to determine what proportion, if any, of the reported
5 ranges are related to operator competency and what is due to other factors.
6 Operator competency may also be captured to some extent in the rate of
7 successful visualisations assumed in the model, though again, it is not
8 possible to quantify based on the available evidence, what proportion of failed
9 procedures is due to the operator.

10

11 Another potential limitation of the model as presented here is the choice of
12 outcome measure. The preferred methodology according to the NICE
13 technical manual is to present outcomes in terms of the quality adjusted life
14 year (QALY). Given the range of pathologies under consideration, and the
15 associated range of treatment pathways, the information requirements to
16 estimate the true cost per QALY of each diagnostic method was beyond the
17 scope of the guideline. This may have some influence over the results, as
18 some patients may undergo unnecessary treatment, while others will not be
19 given required treatment, based on false results following diagnosis. By
20 measuring the results in cost per correct diagnosis, the model may not reflect
21 the true long-term costs and outcomes associated with each diagnostic
22 method.

23

24 Not measuring the outcome of the model in QALYs may also inaccurately
25 reflect the quality of life gain or loss in the short-term, as the chosen outcome

1 does not account for the dis-quality of life of undergoing an invasive diagnostic
2 procedure. This may be reflected to a certain extent in the rates of failure, as
3 the more invasive procedures are successfully completed less often than the
4 less invasive procedures. Although this is unlikely to have a bearing on the
5 longer-term analysis incorporating the full effect of treatment following
6 diagnosis, in the absence of such evidence it must be considered.

7

8 A final limitation concerns the uncertainty of the cost and effectiveness
9 parameters assumed in the analysis of saline-infused sonography. This
10 procedure, though used in other European countries and the United States, is
11 uncommon within the NHS. As a result, there is a shortage of high-quality,
12 UK based evidence regarding its accuracy and cost. Although the sensitivity
13 analysis suggests that under certain, limited, scenarios it may be cost-
14 effective when compared with transvaginal sonography, until further research
15 is undertaken, it cannot be considered a cost-effective option for the diagnosis
16 of intrauterine pathologies in women with heavy menstrual bleeding.

17

1 **Appendix B Competencies**

2 Competencies of clinicians performing procedures to treat HMB were
 3 considered within a framework based on existing models of quality assurance,
 4 that is with consideration of inputs (how competence is achieved);
 5 process/service (how competence is maintained); and how it is measured
 6 (e.g. auditing competence based on quality standards). This framework was
 7 not meant to be exclusive, and if other factors appeared relevant then they
 8 would be included.

9

10 **Becoming competent - Training standards**

11 The process for an individual to become competent in a procedure is usually
 12 based upon them undergoing suitable education and training. Given that
 13 there can be a wide variation in the standards of education and training
 14 courses provided, these courses must be recognised by regulatory or
 15 governing bodies as providing training and education to a suitable level.

16

17 The results of the literature search provided very limited data, especially on
 18 training standards. This is unsurprising given that most training standards are
 19 published by governing bodies rather than as research articles. Relevant
 20 governing bodies were contacted about education and training standards:
 21 RCOG, RCR and BSGE. In addition, the GDG also provided information on
 22 training and education.

23

24 In relation to surgical skills, the GDG outlined a series of basic requirements:

- 1 ▪ Knowledge
- 2 ▪ Specific indications for intervention
- 3 ▪ Required preparation for intervention including preoperative
- 4 investigations
- 5 ▪ Outcomes and complications of proposed procedure
- 6 ▪ Anatomy relevant to procedure
- 7 ▪ Steps involved in procedure
- 8 ▪ Knowledge of alternative operative strategies if difficulties are
- 9 encountered
- 10 ▪ Potential complications
- 11 ▪ Outcomes of procedure
- 12 ▪ Likely post-procedure progress
- 13 ▪ Physiological and pathological changes in condition as a result of the
- 14 procedure
- 15
- 16 Other generic skills
- 17 ▪ Be able to explain procedures and possible outcomes to patients and
- 18 family and take informed consent
- 19 ▪ Possess the necessary hand eye dexterity to complete the procedure
- 20 safely and efficiently, demonstrating appropriate use of assistance
- 21 ▪ Communicate effectively with and manage the operative team
- 22 ▪ Assess the patient for appropriate management options.
- 23 ▪ Assess the patient for physiological parameters and be able to
- 24 intervene appropriately to deal with changing parameters
- 25 ▪ Ability to prioritise interventions

1

2 Attitude

- 3 ▪ Demonstrate interest in, knowledge of, and commitment to specialty
- 4 ▪ Recognise when to ask for advice from others
- 5 ▪ Demonstrate commitment to the multidisciplinary team working with
- 6 other clinicians involved in the care of women with HMB.
- 7 ▪ Surgeons should participate in local and national audit.
- 8 ▪ If a surgeon undertakes any new class of procedure for which he / she
- 9 does not have appropriate training then he / she should seek formal
- 10 training through a process of mentoring. This includes appropriate
- 11 training of the surgical team.
- 12 ▪ Before undertaking new procedures, clinicians must notify their Trust's
- 13 clinical governance committee, and the audit of these new procedures
- 14 should be appraised annually.
- 15 ▪ A robust risk management structure must be in place to facilitate
- 16 reporting of adverse events.
- 17 ▪ Attention should be given to ensuring correct and complete coding of
- 18 procedures for national audit programmes
- 19 ▪ Before utilising new materials or devices in previously established
- 20 procedures, the Trust's clinical governance committee should be
- 21 informed.
- 22 ▪ Any intention to undertake an evaluation of a new procedure should be
- 23 registered with a relevant clinical trials database.

- 1 ▪ The development of new techniques (see below) or modifications of
2 established techniques should receive appropriate local ethical and
3 clinical governance approval.
- 4 ▪ A clinician who encounters a serious adverse event related to the use
5 of a device or implant in the treatment of HMB should notify the
6 Medicines and Healthcare products Regulatory Agency (MHRA),
7 through its Serious Adverse Event (SAE) reporting process.
- 8 ▪ New procedures / classes of procedure should be notified to the
9 Interventional Procedures Programme at NICE through the NICE
10 website.
- 11 ▪ Clinicians should see enough patients per annum to maintain both non
12 operative and operative skills.

13
14 In addition, education and training covers clinicians committing to continuing
15 medical education in order to maintain knowledge and skills.

17 **Maintaining competence**

18 Maintaining competence in a procedure requires two main elements: 1)
19 continuing training and education; 2) continued experience of procedure in
20 practice.

22 **Continuing education**

Continuing education and training is a statutory requirement in many posts. The same skills that were outlined above, for primary education and training, apply to continuing education and training.

Volume-outcome

The necessary surgical volume of any procedure required to maintain competence, is often inadequately defined. Volume-outcome does not relate to a learning curve (which is covered by training and education), but to maintenance of skills and standards of the individual and the hospital. The volume-outcome relationship has been considered in many clinical areas, such as cardiology, gastroenterology, orthopaedics, ophthalmology and breast cancer surgery, but little evaluation has been undertaken in relation to HMB.

In systematic reviews of this research, many methodological concerns have been raised over what is considered to be a heterogeneous body of research, consisting of observational studies. Most studies retrospectively analyse routinely collected data, and are not designed to analyse the complex volume-outcome relationship, which leads to many problems when interpreting the data, namely: ⁵⁵⁴⁻⁵⁵⁶

- inadequate consideration of confounders such as the effects of differences in case-mix and appropriateness of case selection on outcomes
- volume can relate to hospital or operator volume
- narrow outcomes used in most studies, usually adverse (e.g. inpatient or 30-day mortality)

- 1 ▪ thresholds for definitions of high and low volume across and within
- 2 procedures differ
- 3 ▪ causality: it is unclear whether high volume-improved outcomes
- 4 relationships result from greater experience or whether the highest
- 5 referral rate tends to be to those clinicians or centres who have the
- 6 best results

7

8 Hospital volume and operator volume may both be important, and the relative
9 importance may vary from one procedure to another. For some procedures
10 (e.g. trauma related reconstruction) it may be the total amount of relevant
11 surgery that is most important rather than the specific number of particular
12 procedures. Complexity of procedures, and whether their use is
13 commonplace, also influences whether a difference in outcomes can be seen
14 for a given volume.

15

16 Although the evidence tends to suggest that higher volume is associated with
17 better outcomes, the consistency and size of the effect varies for different
18 procedures. A systematic review of 135 studies found a significant
19 association between higher volume (hospital or surgeon) and better outcomes
20 in about 70% of studies; none of the studies found a significant association
21 between higher volume of any type of surgery and poorer outcome.⁵⁵⁵ In
22 these studies, the definition of low or high volume varied according to the
23 procedure, with median low volumes of up to 100 to 200 for coronary
24 angioplasty or coronary artery bypass graft surgery; with median low volume

1 values ranging from 1 to 73 for other procedures described (mainly in the
2 region of 10 to 30).⁵⁵⁵

3

4 Secondary surgery is unusual and can be technically challenging, and a
5 centralisation argument probably applies. The centralisation argument holds
6 that “practise makes perfect”, so concentration of cases into one centre that
7 can carry out larger numbers of procedures will result in higher standards not
8 just of technical surgery but the whole post procedural care team will become
9 familiar with routine and avoid morbidity.

10

11 **Monitoring competencies**

12 The final area involves outlining the standards by which competence in
13 undertaking a particular intervention can be monitored. Audit standards for
14 competencies should be based upon

- 15 ▪ Ensuring that recognised education and training has been undertaken
- 16 ▪ Ensuring that continuing education and training is undertaken
- 17 ▪ Ensuring a minimum level of procedures are undertaken to maintain
18 competence
- 19 ▪ Ensuring outcomes of procedures are within expected ranges

20

Appendix C Guideline Questions

Background questions

1. How is HMB defined?
2. What risk factors are associated with developing HMB?
3. How is clinical effectiveness of treatment for HMB defined?
4. What impact does HMB have on quality of life of the women? (Why do women consult for HMB?)
5. What are the current trends in treatment for HMB in the UK?

4.3.a. The guideline will provide advice on patient educational interventions and information provision to improve patient satisfaction.

4.3.b. The guideline will provide advice on diagnosis of women presenting with HMB, including guidance on appropriate investigations and referral, and the cost-effectiveness of undertaking such investigations.

6. What are the indications for, effectiveness of, and cost-effectiveness of menstrual blood loss estimation in the diagnosis and management of HMB?
7. What is the effectiveness of patient education/ information provision/ counselling on patient satisfaction with treatment for HMB?
8. How much should patient choice influence management?
9. Do lifestyle indications/interventions affect HMB?
10. What questions need to be asked in routine history taking for HMB?

4.3.b. The guideline will provide advice on diagnosis of women presenting with HMB, including guidance on appropriate investigations and referral, and the cost-effectiveness of undertaking such investigations.

11. Physical examination on women with HMB?
12. What are the indications for, effectiveness of, and cost-effectiveness of imaging for excluding other conditions?

1 13. What are the indications for, effectiveness of, and cost-effectiveness of
2 tests for excluding other conditions?

3 14. What are the indications for, effectiveness of, and cost-effectiveness of
4 a full blood count to test for anaemia?

5
6 4.3.c. The guideline will provide advice on the medical management of HMB,
7 including short and long-term outcomes, adverse events, cost-effectiveness
8 and subsequent treatment.

9 15. What are the a) indications for, b) effectiveness of, and c) cost-
10 effectiveness using antifibrinolytics in HMB?

11 16. What are the a) indications for, b) effectiveness of, and c) cost-
12 effectiveness of using NSAIDs in HMB?

13 17. What are the a) indications for, b) effectiveness of, and c) cost-
14 effectiveness of using Etamsylate in HMB?

15 18. What are the a) indications for, b) effectiveness of, and c) cost-
16 effectiveness of using combined oral contraceptive pill at treating
17 HMB?

18 19. What are the a) indications for, b) effectiveness of, and c) cost-
19 effectiveness of using oral progestogens at treating HMB?

20 20. What are the a) indications for, b) effectiveness of, and c) cost-
21 effectiveness of using injected/depo progestogens at treating HMB

22 21. What are the a) indications for, b) effectiveness of, and c) cost-
23 effectiveness of using intrauterine levonorgestrel-releasing systems at
24 treating HMB?

25 22. What are the a) indications for, b) effectiveness of, and c) cost-
26 effectiveness of using HRT in treating HMB

27 23. Medical management of HMB using other pharmaceutical
28 interventions?

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24. What are the a) indications for, b) effectiveness of, and c) cost-effectiveness of using Gonadotrophin-releasing hormone analogue at treating HMB?

4.3.d. The guideline will provide advice on the indications for referral to secondary care management.

25. What are the indications for surgery?

4.3.e. The guideline will provide advice to determine if, and when, surgical procedures are most appropriate.

26. Are there situations where non-pharmaceutical treatment should not be the first line of treatment for HMB?

4.3.f. The guideline will provide advice on operative procedures used for endometrial ablation/resection in HMB, including short- and long-term outcomes, cost-effectiveness, adverse events, and subsequent treatment.

27. What are the a) indications for, b) effectiveness of, and c) cost-effectiveness of using D & C for treating HMB?

28. What are the a) indications for, b) effectiveness of, and c) cost-effectiveness of using endometrial ablation/resection for treating HMB?

4.3.g. The guideline will provide advice on operative procedures used for uterine artery embolisation in HMB, including short- and long-term outcomes, cost-effectiveness, adverse events, and subsequent treatment.

29. What are the a) indications for, b) effectiveness of, and c) cost-effectiveness of using radiological interventions for use in HMB?

1
2 4.3.h. The guideline will provide advice on operative procedures and other
3 techniques used for hysterectomy and myomectomy in HMB, including short-
4 and long-term outcomes, adverse events, and subsequent treatment. This
5 will include guidance on minimal access techniques (laparoscopically).

6 30. What are the a) indications for, b) effectiveness of, and c) cost-
7 effectiveness of using myomectomy for HMB?

8 31. Are there any indications for using hysterectomy as first line treatment
9 for HMB?

10 32. What are the a) indications for, b) effectiveness of, and c) cost-
11 effectiveness of using hysterectomy for treating HMB?
12

13 4.3.i. When hysterectomy is the most appropriate option, issues relating to the
14 removal of healthy ovaries will be examined.

15 33. What are the a) indications for, b) effectiveness of, and c) cost-
16 effectiveness of removing ovaries during hysterectomy versus not
17 removing?
18

19 4.3.j. The competencies required by practitioners who wish to carry out
20 surgical techniques and other interventions, such as UAE will be provided.

21 34. What are the competencies required by practitioners who wish to carry
22 out surgical techniques and other interventions for HMB?

23 35. Competencies for investigations?
24

Appendix D Declarations of Interest

Anna Belli – Conference funding from Boston Scientific, funding to department for research fellow from Johnson & Johnson.

Dianne Crowe – No interests declared.

Sean Duffy – Non-current interest: Research funding for department from Gynaecare, Conceptus and Chiroxia.

Sarah Gray – Advisory Board for non hormonal therapies for menopausal symptoms for Wyeth. Travel expenses to attend scientific meetings from Organon and Wyeth.

Yasmin Gunaratnam – No interests to declare.

Mary-Anne Lumsden – No interests declared.

Klim McPherson – No interests declared.

Jane Preston – No interests to declare.

David Parkin – Non-current interests: Research funding to department and for conference attendance by Microsulis PLC.

Mark Shapley – Current personal grants: Medical Officer from Exel Logistics.

Bridgette York – No interests declared.

References

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Reference List

1. Ware JJ and Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992; 30:473-83.
2. NHS Executive. Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS. 1996. London, HMSO.
3. National Institute for Clinical Excellence. Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers. London: National Institute for Clinical Evidence; 2005.
4. Oxman AD, Sackett DL, and Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1993; 270:(17)2093-5.
5. Guyatt GH, Sackett DL, and Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1993; 270:(21)2598-601.
6. Guyatt GH, Sackett DL, and Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1994; 271:(1)59-63.
7. Jaeschke R, Guyatt GH, and Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1994; 271:(9)703-7.
8. Jaeschke R, Guyatt G, and Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1994; 271:(5)389-91.
9. Sackett DL, Straus SE, Richardson WS, Rosenberg W, and Haynes RB. Evidence-based medicine. How to practice and teach EBM. Second ed. Edinburgh: Churchill Livingstone; 2000.

- 1 10. Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline
2 developers' handbook. No. 50. Edinburgh: Scottish Intercollegiate
3 Guideline Network; 2001.
- 4 11. Drummond MF, O'Brien B, Stoddart GL, and Torrance GW. Methods
5 for the economic evaluation of health care programmes. Oxford
6 University Press; 1997.
- 7 12. Faculty of Family Planning and Reproductive Health Care CEU.
8 FFPRHC Guidance (October 2003): First prescription of combined
9 oral contraception.[erratum appears in J Fam Plann Reprod Health
10 Care. 2004 Jan;30(1):63]. *Journal of Family Planning and*
11 *Reproductive Health Care* 2003; 29:(4)209-22.
- 12 13. Faculty of Family Planning and Reproductive Health Care CEU.
13 FFPRHC Guidance (October 2003): First prescription of combined
14 oral contraception.[erratum appears in J Fam Plann Reprod Health
15 Care. 2004 Jan;30(1):63]. *Journal of Family Planning and*
16 *Reproductive Health Care* 2003; 29:(4)209-22.
- 17 14. Faculty of Family Planning and Reproductive Health Care CEU.
18 FFPRHC Guidance (October 2003): First prescription of combined
19 oral contraception.[erratum appears in J Fam Plann Reprod Health
20 Care. 2004 Jan;30(1):63]. *Journal of Family Planning and*
21 *Reproductive Health Care* 2003; 29:(4)209-22.
- 22 15. Faculty of Family Planning and Reproductive Health Care CEU.
23 FFPRHC Guidance (October 2003): First prescription of combined
24 oral contraception.[erratum appears in J Fam Plann Reprod Health
25 Care. 2004 Jan;30(1):63]. *Journal of Family Planning and*
26 *Reproductive Health Care* 2003; 29:(4)209-22.
- 27 16. Snowden R. The statistical analysis of menstrual bleeding patterns.
28 *Journal of Biosocial Science* 1977; 9:107-20.
- 29 17. Harlow SD and Campbell BC. Host factors that influence the duration
30 of menstrual bleeding. *Epidemiology* 1994; 5:(3)352-5.
- 31 18. Campbell H, Edstrom K, and Engstrom L. World Health Organization
32 multicenter study on menstrual and ovulatory patterns in adolescent
33 girls. II. Longitudinal study of menstrual patterns in the early
34 postmenarcheal period, duration of bleeding episodes and menstrual
35 cycles. *Journal of Adolescent Health Care* 1986; 7:(4)236-44.
- 36 19. Treloar AE, Boynton RE, Behn BG *et al.* Variation of the human
37 menstrual cycle through reproductive life. *International Journal of*
38 *Fertility* 1967; 12:(1 Pt 2)77-126.
- 39 20. Matsumoto S, Nogami Y, and Ohkuri S. Statistical studies on
40 menstruation; a criticism on the definition of normal menstruation.
41 *Gunma Journal of Medical Science* 1962; 11:294-318.

- 1 21. Cazzola A. A profile of the female cycle length. *Statistica* 1994;
2 54:(4)455-79.
- 3 22. Monari P and Montanari A. Length of menstrual cycles and their
4 variability. *Genus* 1998; 54:(3-4)95-118.
- 5 23. Kato I, Toniolo P, Koenig KL *et al.* Epidemiologic correlates with
6 menstrual cycle length in middle aged women. *European Journal of*
7 *Epidemiology* 1999; 15:(9)809-14.
- 8 24. Thomas KD, Okonofua FE, and Chiboka O. A study of the menstrual
9 patterns of adolescents in Ile-Ife, Nigeria. *International Journal of*
10 *Gynaecology and Obstetrics* 1990; 33:(1)31-4.
- 11 25. Jeyaseelan L, Antonisamy B, and Rao PS. Pattern of menstrual cycle
12 length in south Indian women: a prospective study. *Social Biology*
13 1992; 39:(3-4)306-9.
- 14 26. Odujinrin OM and Ekunwe EO. Epidemiologic survey of menstrual
15 patterns amongst adolescents in Nigeria. *West African Journal of*
16 *Medicine* 1991; 10:(3-4)244-9.
- 17 27. Munster K, Schmidt L, and Helm P. Length and variation in the
18 menstrual cycle - A cross-sectional study from a Danish county.
19 *British Journal of Obstetrics and Gynaecology* 1992; 99:(5)422-9.
- 20 28. Chiazze L, Jr., Brayer FT, Macisco JJ, Jr. *et al.* The length and
21 variability of the human menstrual cycle. *JAMA: the journal of the*
22 *American Medical Association* 1968; 203:(6)377-80.
- 23 29. Harlow SD and Zeger SL. An application of longitudinal methods to
24 the analysis of menstrual diary data. *Journal of Clinical Epidemiology*
25 1991; 44:(10)1015-25.
- 26 30. Hallberg L, Hogdahl AM, Nilsson L *et al.* Menstrual blood loss--a
27 population study. Variation at different ages and attempts to define
28 normality. *Acta Obstetrica et Gynecologica Scandinavica* 1966;
29 45:(3)320-51.
- 30 31. Janssen CA, Scholten PC, and Heintz AP. Reconsidering
31 menorrhagia in gynecological practice. Is a 30-year-old definition still
32 valid? *European Journal of Obstetrics, Gynecology, and*
33 *Reproductive Biology* 1998; 78:(1)69-72.
- 34 32. Cole SK, Billewicz WZ, and Thomson AM. Sources of variation in
35 menstrual blood loss. *Journal of Obstetrics and Gynaecology of the*
36 *British Commonwealth* 1971; 78:(10)933-9.
- 37 33. Payson M, Leppert P, and Segars J. Epidemiology of myomas.
38 *Obstetrics and Gynecology Clinics of North America* 2006; 33:(1)1-
39 11.

- 1 34. Cramer SF and Patel A. The frequency of uterine leiomyomas.
2 *American Journal of Clinical Pathology* 1990; 94:(4)435-8.
- 3 35. Cramer DW. Epidemiology of myomas. *Seminars in Reproductive*
4 *Endocrinology* 1992; 10:(4)320-4.
- 5 36. Lurie S, Piper I, Woliovitch I *et al.* Age-related prevalence of
6 sonographically confirmed uterine myomas. *Journal of Obstetrics &*
7 *Gynaecology*. 2005; 25:(1)42-4.
- 8 37. Kjerulff KH, Langenberg P, Seidman JD *et al.* Uterine leiomyomas.
9 Racial differences in severity, symptoms and age at diagnosis.
10 *Journal of Reproductive Medicine* 1996; 41:(7)483-90.
- 11 38. Wegienka G, Baird DD, Hertz-Picciotto I *et al.* Self-reported heavy
12 bleeding associated with uterine leiomyomata. *Obstetrics and*
13 *Gynecology* 2003; 101:(3)431-7.
- 14 39. Sulaiman S, Khaund A, McMillan N *et al.* Uterine fibroids - do size
15 and location determine menstrual blood loss? *European Journal of*
16 *Obstetrics and Gynecology* 2004; 115:(1)85-9.
- 17 40. Vercellini P, Vendola N, Ragni G *et al.* Abnormal uterine bleeding
18 associated with iron-deficiency anemia. Etiology and role of
19 hysteroscopy. *Journal of Reproductive Medicine* 1993; 38:(7)502-4.
- 20 41. Fraser IS. Hysteroscopy and laparoscopy in women with
21 menorrhagia. *American Journal of Obstetrics and Gynecology* 1990;
22 162:(5)1264-9.
- 23 42. Emanuel MH, Verdel MJC, Stas H *et al.* An audit of true prevalence
24 of intra-uterine pathology: The hysteroscopic findings controlled for
25 patient selection in 1202 patients with abnormal uterine bleeding.
26 *Gynaecological Endoscopy* 1995; 4:(4)237-41.
- 27 43. Utman N and Mumtaz A. Pubertal menorrhagia: Causes and
28 management. *Medical Forum Monthly* 2002; 13:(6)162-4.
- 29 44. Belsey EM and Pinol AP. Menstrual bleeding patterns in untreated
30 women. Task Force on Long-Acting Systemic Agents for Fertility
31 Regulation. *Contraception* 1997; 55:(2)57-65.
- 32 45. Cote I, Jacobs P, and Cumming DC. Use of health services
33 associated with increased menstrual loss in the United States.
34 *American Journal of Obstetrics and Gynecology* 2003; 188:(2)343-8.
- 35 46. Shapley M, Jordan K, and Croft PR. An epidemiological survey of
36 symptoms of menstrual loss in the community. *British Journal of*
37 *General Practice* 2004; 54:(502)359-63.

- 1 47. Higham JM and Shaw RW. Clinical associations with objective
2 menstrual blood volume. *European Journal of Obstetrics,*
3 *Gynecology, and Reproductive Biology* 1999; 82:(1)73-6.
- 4 48. Janssen CA, Scholten PC, and Heintz AP. Menorrhagia--a search for
5 epidemiological risk markers. *Maturitas* 1997; 28:(1)19-25.
- 6 49. Kritz-Silverstein D, Wingard DL, and Garland FC. The association of
7 behavior and lifestyle factors with menstrual symptoms. *Journal of*
8 *Womens Health and Gender-Based Medicine* 1999; 8:(9)1185-93.
- 9 50. Hefnawi F, El Z, and Yacout MM. Physiologic studies of menstrual
10 blood loss. I. Range and consistency of menstrual blood loss in and
11 iron requirements of menstruating Egyptian women. *International*
12 *Journal of Gynecology and Obstetrics* 1979; 17:(4)348-52.
- 13 51. Barer AP and Fowler MD. Blood loss during normal menstruation.
14 *American Journal of Obstetrics and Gynecology* 1936; 31:979-86.
- 15 52. Woo YL, White B, Corbally R *et al.* Von Willebrand's disease: an
16 important cause of dysfunctional uterine bleeding. *Blood Coagulation*
17 *and Fibrinolysis* 2002; 13:(2)89-93.
- 18 53. Shankar M, Lee CA, Sabin CA *et al.* von Willebrand disease in
19 women with menorrhagia: a systematic review. *BJOG: an*
20 *International Journal of Obstetrics and Gynaecology* 2004;
21 111:(7)734-40.
- 22 54. Kadir RA, Economides DL, Sabin CA *et al.* Frequency of inherited
23 bleeding disorders in women with menorrhagia. *Lancet* 1998;
24 351:(9101)485-9.
- 25 55. Rodeghiero F, Castaman G, and Dini E. Epidemiological investigation
26 of the prevalence of von Willebrand's disease. *Blood.* 1987;
27 69:(2)454-9.
- 28 56. Sensky TE and Liu DTY. Endometriosis: Associations with
29 menorrhagia, infertility and oral contraceptives. *International Journal*
30 *of Gynecology and Obstetrics* 1979; 17:(6)573-6.
- 31 57. Mahmood TA and Templeton A. Prevalence and genesis of
32 endometriosis. *Human Reproduction* 1991; 6:(4)544-9.
- 33 58. Gordley LB, Lemasters G, Simpson SR *et al.* Menstrual disorder and
34 occupational, stress, and racial factors among military personnel.
35 *Journal of Occupational and Environmental Medicine* 2000;
36 42:(9)871-81.
- 37 59. Harlow SD, Campbell B, Lin X *et al.* Ethnic differences in the length of
38 the menstrual cycle during the postmenarcheal period. *American*
39 *Journal of Epidemiology* 1997; 146:(7)572-80.

- 1 60. Rybo G. Menstrual blood loss in relation to parity and menstrual
2 pattern. *Acta Obstetrica et Gynecologica Scandinavica* 1966;
3 45:(Suppl 7)25-45.
- 4 61. Zielhuis GA, Gijsen R, and Van der Gulden JWJ. Menstrual disorders
5 among dry-cleaning workers. *Scandinavian Journal of Work,*
6 *Environment and Health* 1989; 15:(3)238.
- 7 62. Hartz AJ, Barboriak PN, Wong A *et al.* The association of obesity with
8 infertility and related menstrual abnormalities in women. *International*
9 *Journal of Obesity and Related Metabolic Disorders* 1979; 3:(1)57-73.
- 10 63. Ballinger CB, Smith AH, and Hobbs PR. Factors associated with
11 psychiatric morbidity in women--a general practice survey. *Acta*
12 *Psychiatrica Scandinavica* 1985; 71:(3)272-80.
- 13 64. Shapley M, Jordan K, and Croft PR. Increased vaginal bleeding: the
14 reasons women give for consulting primary care. *Journal of*
15 *Obstetrics and Gynaecology* 2003; 23:(1)48-50.
- 16 65. Shapley M, Jordan K, and Croft PR. Why women consult with
17 increased vaginal bleeding: a case-control study. *British Journal of*
18 *General Practice* 2002; 52:(475)108-13.
- 19 66. Shapley M, Croft PR, McCarney R *et al.* Does psychological status
20 predict the presentation in primary care of women with a menstrual
21 disturbance? *British Journal of General Practice* 2000; 50:(455)491-2.
- 22 67. Gath D, Osborn M, Bungay G *et al.* Psychiatric disorder and
23 gynaecological symptoms in middle aged women: a community
24 survey. *British Medical Journal Clinical Research Ed.* 1987;
25 294:(6566)213-8.
- 26 68. Hurskainen R, Aalto AM, Teperi J *et al.* Psychosocial and other
27 characteristics of women complaining of menorrhagia, with and
28 without actual increased menstrual blood loss. *BJOG : an*
29 *international journal of obstetrics and gynaecology* 2001; 108:(3)281-
30 5.
- 31 69. Greenberg M. The meaning of menorrhagia: An investigation into the
32 association between the complaint of menorrhagia and depression.
33 *Journal of Psychosomatic Research* 1983; 27:(3)209-14.
- 34 70. Granleese J. Personality, sexual behaviour and menstrual symptoms:
35 their relevance to clinically presenting with menorrhagia. *Person Invid*
36 *Diff* 1990; 11:(4)379-90.
- 37 71. Critchley HO, Warner P, Lee AJ *et al.* Evaluation of abnormal uterine
38 bleeding: comparison of three outpatient procedures within cohorts
39 defined by age and menopausal status. *Health Technology*
40 *Assessment* 2001; 8:(34)iii, 1-iv, 139.

- 1 72. Vercellini P, Cortesi I, Oldani S *et al.* The role of transvaginal
2 ultrasonography and outpatient diagnostic hysteroscopy in the
3 evaluation of patients with menorrhagia. *Human reproduction*
4 (Oxford, England) 1997; 12:(8)1768-71.
- 5 73. Nagele F, O'Connor H, Davies A *et al.* 2500 Outpatient diagnostic
6 hysteroscopies. *Obstetrics & Gynecology.* 1996; 88:(1)87-92.
- 7 74. MacKenzie IZ and Bibby JG. Critical assessment of dilatation and
8 curettage in 1029 women. *Lancet.* 1978; 2:(8089)566-8.
- 9 75. Bronz L, Suter T, and Rusca T. The value of transvaginal sonography
10 with and without saline instillation in the diagnosis of uterine
11 pathology in pre- and postmenopausal women with abnormal
12 bleeding or suspect sonographic findings. *Ultrasound in Obstetrics*
13 *and Gynecology* 1997; 9:(1)53-8.
- 14 76. Valle RF. Hysteroscopic evaluation of patients with abnormal uterine
15 bleeding. *Surgery, Gynecology and Obstetrics* 1981; 153:(4)521-6.
- 16 77. Alexopoulos ED, Fay TN, and Simonis CD. A review of 2581 out-
17 patient diagnostic hysteroscopies in the management of abnormal
18 uterine bleeding. *Gynaecological Endoscopy* 1999; 8:(2)105-10.
- 19 78. Stovall TG, Ling FW, and Morgan PL. A prospective, randomized
20 comparison of the Pipelle endometrial sampling device with the
21 Novak curette. *American Journal of Obstetrics & Gynecology.* 1991;
22 165:(5 Part 1)1287-90.
- 23 79. Ash SJ, Farrell SA, and Flowerdew G. Endometrial biopsy in DUB.
24 *Journal of Reproductive Medicine.* 1996; 41:(12)892-6.
- 25 80. Fedele L, Bianchi S, Dorta M *et al.* Transvaginal ultrasonography in
26 the diagnosis of diffuse adenomyosis. *Fertility and Sterility* 1992;
27 58:(1)94-7.
- 28 81. Vercellini P, Cortesi I, De GO *et al.* Transvaginal ultrasonography
29 versus uterine needle biopsy in the diagnosis of diffuse adenomyosis.
30 *Human Reproduction* 1998; 13:(10)2884-7.
- 31 82. Clevenger-Hoeft M, Syrop CH, Stovall DW *et al.* Sonohysterography
32 in premenopausal women with and without abnormal bleeding.
33 *Obstetrics and Gynecology* 1999; 94:(4)516-20.
- 34 83. Motashaw ND and Dave S. Diagnostic and therapeutic hysteroscopy
35 in the management of abnormal uterine bleeding. *Journal of*
36 *Reproductive Medicine* 1990; 35:(6)616-20.
- 37 84. Allen DG, Correy JF, and Marsden DE. Abnormal uterine bleeding
38 and cancer of the genital tract. *Australian and New Zealand Journal*
39 *of Obstetrics and Gynaecology* 1990; 30:(1)81-3.

- 1 85. Farquhar CM, Lethaby A, Sowter M *et al.* An evaluation of risk factors
2 for endometrial hyperplasia in premenopausal women with abnormal
3 menstrual bleeding. *American Journal of Obstetrics and Gynecology*
4 1999; 181:(3)525-9.
- 5 86. Loffer FD. Hysteroscopy with selective endometrial sampling
6 compared with D&C for abnormal uterine bleeding: the value of a
7 negative hysteroscopic view. *Obstetrics & Gynecology* 1989;
8 73:(1)16-20.
- 9 87. Decloedt JF and Fenton DW. Outpatient hysteroscopy: Indications
10 and hysteroscopic findings in pre- and postmenopausal patients.
11 *Gynaecological Endoscopy* 1999; 8:(3)137-41.
- 12 88. Hammouda AA. Premenopausal and menopausal dysfunctional
13 uterine bleeding. An analysis of 660 cases. *International Surgery*
14 1967; 47:(2)194-8.
- 15 89. Office for National Statistics. Cancer statistics registrations.
16 Registrations of cancer diagnosed in England, 2003. London: Office
17 for National Statistics; 2005.
- 18 90. Scottish Cancer Registry IS. Cancer of corpus uteri. Lifetime risk of
19 developing cancer (up to the age of 90), Scotland: 1997-2001.
20 Edinburgh: ISD Scotland; 2006.
- 21 91. National Cancer Institute DSRPCSB. SEER 17 Incidence and
22 Mortality, 2000-2003, with Kaposi Sarcoma and Mesothelioma. 2006.
- 23 92. The management of menorrhagia in secondary care: National
24 Evidence-Based Clinical Guidelines. RCOG Press; 1999.
- 25 93. Schmeler KM, Soliman PT, Sun CC *et al.* Endometrial cancer in
26 young, normal-weight women. *Gynecologic Oncology* 2005;
27 99:(2)388-92.
- 28 94. Soliman PT, Oh JC, Schmeler KM *et al.* Risk factors for young
29 premenopausal women with endometrial cancer. *Obstetrics and*
30 *Gynecology* 2005; 105:(3)575-80.
- 31 95. Quinn MA, Kneale BJ, and Fortune DW. Endometrial carcinoma in
32 premenopausal women: a clinicopathological study. *Gynecologic*
33 *Oncology* 1985; 20:(3)298-306.
- 34 96. Parslov M, Lidegaard O, Klintorp S *et al.* Risk factors among young
35 women with endometrial cancer: a Danish case-control study.
36 *American Journal of Obstetrics and Gynecology* 2000; 182:(1 Pt
37 1)23-9.
- 38 97. National Institute for Health and Clinical Excellence. Referral
39 Guidelines for Suspected Cancer. 2005. London, National Institute
40 for Health and Clinical Excellence.

- 1 98. Clark TJ, Khan KS, Foon R *et al.* Quality of life instruments in studies
2 of menorrhagia: a systematic review. *European Journal of Obstetrics,*
3 *Gynecology, and Reproductive Biology* 2002; 104:(2)96-104.
- 4 99. Jenkinson C, Peto V, and Coulter A. Making sense of ambiguity:
5 evaluation of internal reliability and face validity of the SF 36
6 questionnaire in women presenting with menorrhagia. *Quality in*
7 *Health Care* 1996; 5:(1)9-12.
- 8 100. Mansfield PK, Voda A, and Allison G. Validating a pencil-and-paper
9 measure of perimenopausal menstrual blood loss. *Women's Health*
10 *Issues* 2004; 14:(6)242-7.
- 11 101. Ruta DA, Garratt AM, Chadha YC *et al.* Assessment of patients with
12 menorrhagia: How valid is a structured clinical history as a measure
13 of health status? *Quality of Life Research* 1995; 4:(1)33-40.
- 14 102. Shaw RW, Brickley MR, Evans L *et al.* Perceptions of women on the
15 impact of menorrhagia on their health using multi-attribute utility
16 assessment. *British Journal of Obstetrics and Gynaecology* 1998;
17 105:(11)1159.
- 18 103. Abbott JA, Hawe J, and Garry R. Quality of life should be considered
19 the primary outcome for measuring success of endometrial ablation.
20 *Journal of the American Association of Gynecologic Laparoscopists*
21 2003; 10:(4)491-5.
- 22 104. Cooper KG, Bain C, and Parkin DE. Comparison of microwave
23 endometrial ablation and transcervical resection of the endometrium
24 for treatment of heavy menstrual loss: a randomised trial. *Lancet*
25 1999; 354:(9193)1859-63.
- 26 105. Hawe J, Abbott J, Hunter D *et al.* A randomised controlled trial
27 comparing the Cavaterm endometrial ablation system with the
28 Nd:YAG laser for the treatment of dysfunctional uterine bleeding.
29 *BJOG: an International Journal of Obstetrics and Gynaecology* 2003;
30 110:(4)350-7.
- 31 106. Hurskainen R, Teperi J, Rissanen P *et al.* Clinical Outcomes and
32 Costs with the Levonorgestrel-Releasing Intrauterine System or
33 Hysterectomy for Treatment of Menorrhagia: Randomized Trial 5-
34 Year Follow-up. *JAMA: the journal of the American Medical*
35 *Association* 2004; 291:(12)1456-63.
- 36 107. Hurskainen R, Teperi J, Rissanen P *et al.* Quality of life and cost-
37 effectiveness of levonorgestrel-releasing intrauterine system versus
38 hysterectomy for treatment of menorrhagia: a randomised trial. [see
39 comments]. *Lancet* 2001; 357:(9252)273-7.

- 1 108. Gath D, Cooper P, and Day A. Hysterectomy and psychiatric
2 disorder: I. Levels of psychiatric morbidity before and after
3 hysterectomy. *British Journal of Psychiatry* 1982; 140:335-42.
- 4 109. Smith WJ, Upton E, Shuster EJ *et al.* Patient satisfaction and disease
5 specific quality of life after uterine artery embolization. *American*
6 *Journal of Obstetrics and Gynecology* 2004; 190:(6)1697-703.
- 7 110. Byles JE, Hanrahan PF, and Schofield MJ. 'It would be good to know
8 you're not alone': The health care needs of women with menstrual
9 symptoms. *Family Practice* 1997; 14:(3)249-54.
- 10 111. Chapple A. Menorrhagia: women's perceptions of this condition and
11 its treatment. *Journal of Advanced Nursing* 1999; 29:(6)1500-6.
- 12 112. Marshall J. An exploration of women's concerns about heavy
13 menstrual blood loss and their expectations regarding treatment.
14 *Journal of Reproductive and Infant Psychology* 1998; 16:(4)259-76.
- 15 113. Warner PE, Critchley HOD, Lumsden MA *et al.* Menorrhagia II: Is the
16 80-mL blood loss criterion useful in management of complaint of
17 menorrhagia? *American Journal of Obstetrics and Gynecology* 2004;
18 190:(5)1224-9.
- 19 114. Warner PE, Critchley HOD, Lumsden MA *et al.* Menorrhagia I:
20 Measured blood loss, clinical features, and outcome in women with
21 heavy periods - A survey with follow-up data. *American Journal of*
22 *Obstetrics and Gynecology* 2004; 190:(5)1216-23.
- 23 115. Cote I, Jacobs P, and Cumming D. Work loss associated with
24 increased menstrual loss in the United States. *Obstetrics and*
25 *Gynecology* 2002; Vol. 100:(4)683-7.
- 26 116. Mikhail BI. Health-related concerns and experiences of employed
27 perimenopausal women in Alexandria, Egypt. *Health Care for Women*
28 *International* 1985; 17:(2)173-86.
- 29 117. Coulter A, Peto V, and Jenkinson C. Quality of life and patient
30 satisfaction following treatment for menorrhagia. *Family Practice*
31 1994; 11:(4)394-401.
- 32 118. Coulter A, Peto V, and Doll H. Gynaecology: the experience of
33 patients referred to NHS and private clinics. *Health Trends* 1995;
34 27:(2)57-61.
- 35 119. Spies JB, Warren EH, Mathias SD *et al.* Uterine fibroid embolization:
36 measurement of health-related quality of life before and after therapy.
37 *Journal of Vascular and Interventional Radiology* 1999; 10:(10)1293-
38 303.
- 39 120. Cooper KG, Parkin DE, Garratt AM *et al.* A randomised comparison
40 of medical and hysteroscopic management in women consulting a

- 1 gynaecologist for treatment of heavy menstrual loss. *British Journal of*
2 *Obstetrics and Gynaecology* 1997; 104:(12)1360-6.
- 3 121. Learman LA, Summitt Jr RL, Varner RE *et al.* Hysterectomy versus
4 expanded medical treatment for abnormal uterine bleeding: Clinical
5 outcomes in the medicine or surgery trial. *Obstetrics and Gynecology*
6 2004; 103:(5 I)824-33.
- 7 122. Cheyne GA and Shepherd MM. Comparison of chemical and atomic
8 absorption methods for estimating menstrual blood loss. *Journal of*
9 *Medical Laboratory Technology* 1970; 27:(3)350-4.
- 10 123. Shaw ST, Jr., Aaronson DE, and Moyer DL. Quantitation of menstrual
11 blood loss--further evaluation of the alkaline hematin method.
12 *Contraception* 1972; 5:(6)497-513.
- 13 124. van Eijkeren MA, Scholten PC, Christiaens GC *et al.* The alkaline
14 hematin method for measuring menstrual blood loss--a modification
15 and its clinical use in menorrhagia. *European Journal of Obstetrics,*
16 *Gynecology, and Reproductive Biology* 1986; 22:(5-6)345-51.
- 17 125. Vasilenko P, Kraicer PF, Kaplan R *et al.* A new and simple method of
18 measuring menstrual blood loss. *Journal of Reproductive Medicine*
19 1988; 33:(3)293-7.
- 20 126. Janssen CA, Scholten PC, and Heintz AP. A simple visual
21 assessment technique to discriminate between menorrhagia and
22 normal menstrual blood loss. *Obstetrics and Gynecology* 1995;
23 85:(6)977-82.
- 24 127. Pendergrass PB, Scott JN, and Ream LJ. A rapid, noninvasive
25 method for evaluation of total menstrual loss. *Gynecologic and*
26 *Obstetric Investigation* 1984; 17:(4)174-8.
- 27 128. Wyatt KM, Dimmock PW, Walker TJ *et al.* Determination of total
28 menstrual blood loss. *Fertility and Sterility* 2001; 76:(1)125-31.
- 29 129. Rees MC. Role of menstrual blood loss measurements in
30 management of complaints of excessive menstrual bleeding. *British*
31 *Journal of Obstetrics and Gynaecology* 1991; 98:(3)327-8.
- 32 130. Gannon MJ, Day P, Hammadieh N *et al.* A new method for
33 measuring menstrual blood loss and its use in screening women
34 before endometrial ablation. *British Journal of Obstetrics and*
35 *Gynaecology* 1996; 103:(10)1029-33.
- 36 131. Chapple A, May C, and Ling M. Is objective testing for menorrhagia in
37 general practice practical? Results from a qualitative study. *European*
38 *Journal of General Practice* 2001; 7:(1)13-7.
- 39 132. O'Flynn N and Britten N. Menorrhagia in general practice--disease or
40 illness. *Social Science and Medicine* 2000; 50:(5)651-61.

133. Higham JM, O'Brien PM, and Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *British Journal of Obstetrics and Gynaecology* 1990; 97:(8)734-9.
134. Reid PC, Coker A, and Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. *BJOG: an International Journal of Obstetrics and Gynaecology* 2000; 107:(3)320-2.
135. Deeny M and Davis JA. Assessment of menstrual blood loss in women referred for endometrial ablation. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1994; 57:(3)179-80.
136. Barr F, Brabin L, and Agbaje O. A pictorial chart for managing common menstrual disorders in Nigerian adolescents. *International Journal of Gynecology and Obstetrics* 1999; 66:(1)51-3.
137. Snowden R and Christian B. Patterns and perceptions of menstruation. A World Health Organization international collaborative study. London: Croon Helm; 1983.
138. Chimbira TH, Anderson AB, and Turnbull A. Relation between measured menstrual blood loss and patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area. *British Journal of Obstetrics and Gynaecology* 1980; 87:(7)603-9.
139. Fraser IS, McCarron G, and Markham R. A preliminary study of factors influencing perception of menstrual blood loss volume. *American Journal of Obstetrics and Gynecology* 1984; 149:(7)788-93.
140. Heath AL, Skeaff CM, and Gibson RS. Validation of a questionnaire method for estimating extent of menstrual blood loss in young adult women. *Journal of Trace Elements in Medicine and Biology* 1999; 12:(4)231-5.
141. Harlow SD and Campbell OMR. Epidemiology of menstrual disorders in developing countries: A systematic review. *BJOG: an International Journal of Obstetrics and Gynaecology* 2004; 111:(1)6-16.
142. Shapley M and Redman CWE. Assessment of menstrual blood loss using a pictorial chart and endometrial sampling within the community. *Journal of Obstetrics and Gynaecology* 1995; 15:(2)123-4.
143. Santer M, Warner P, and Wyke S. A Scottish postal survey suggested that the prevailing clinical preoccupation with heavy periods does not reflect the epidemiology of reported symptoms and problems. *Journal of Clinical Epidemiology* 2005; 58:(11)1206-10.

- 1 144. Treloar SA, Do KA, O'Connor VM *et al.* Predictors of hysterectomy:
2 an Australian study. *American Journal of Obstetrics and Gynecology*
3 1999; 180:(4)945-54.
- 4 145. Eldred JM and Thomas EJ. Pituitary and ovarian hormone levels in
5 unexplained menorrhagia. *Obstetrics & Gynecology* 1994; 84:(5)775-
6 8.
- 7 146. Haynes PJ, Anderson ABM, and Turnbull AC. Patterns of menstrual
8 blood loss in menorrhagia. *Research and Clinical Forums* 1979;
9 1:(2)73-8.
- 10 147. Krassas GE, Pontikides N, Kaltsas T *et al.* Menstrual disturbances in
11 thyrotoxicosis. *Clinical Endocrinology*. 1994; 40:(5)641-4.
- 12 148. James A, Matchar DB, and Myers ER. Testing for von Willebrand
13 disease in women with menorrhagia: a systematic review. *Obstetrics*
14 *and Gynecology* 2004; 104:(2)381-8.
- 15 149. Claessens EA and Cowell CA. Acute adolescent menorrhagia.
16 *American Journal of Obstetrics and Gynecology* 1981; 139:(3)277-80.
- 17 150. Looker AC, Dallman PR, Carroll MD *et al.* Prevalence of iron
18 deficiency in the United States. *JAMA: the journal of the American*
19 *Medical Association* 1997; 277:(12)973-6.
- 20 151. Andrade AT, Souza JP, Shaw ST, Jr. *et al.* Menstrual blood loss and
21 body iron stores in Brazilian women. *Contraception* 1991; 43:(3)241-
22 9.
- 23 152. Gao J, Zeng S, Sun BL *et al.* Menstrual blood loss and hematologic
24 indices in healthy Chinese women. *Journal of Reproductive Medicine*
25 1987; 32:(11)822-6.
- 26 153. Guyatt GH, Oxman AD, Ali M *et al.* Laboratory diagnosis of iron-
27 deficiency anemia: an overview. *Journal of General Internal Medicine*
28 1992; 7:(2)145-53.
- 29 154. Farquhar C, Ekeroma A, Furness S *et al.* A systematic review of
30 transvaginal ultrasonography, sonohysterography and hysteroscopy
31 for the investigation of abnormal uterine bleeding in premenopausal
32 women. *Acta Obstetrica et Gynecologica Scandinavica* 2003;
33 82:(6)493-504.
- 34 155. Dueholm M, Lundorf E, and Olesen F. Imaging techniques for
35 evaluation of the uterine cavity and endometrium in premenopausal
36 patients before minimally invasive surgery. *Obstetrical and*
37 *Gynecological Survey* 2002; 57:(6)389-403.
- 38 156. Cepni I, Ocal P, Erkan S *et al.* Comparison of transvaginal
39 sonography, saline infusion sonography and hysteroscopy in the

- 1 evaluation of uterine cavity pathologies. *Australian & New Zealand*
2 *Journal of Obstetrics & Gynaecology* 2005; 45:30-5.
- 3 157. De Kroon CD, de Bock GH, Dieben SW *et al.* Saline contrast
4 hysterosonography in abnormal uterine bleeding: a systematic review
5 and meta-analysis. *BJOG: an International Journal of Obstetrics and*
6 *Gynaecology* 2003; 110:(10)938-47.
- 7 158. Clark TJ, Voit D, Gupta JK *et al.* Accuracy of hysteroscopy in the
8 diagnosis of endometrial cancer and hyperplasia: a systematic
9 quantitative review. *JAMA: the journal of the American Medical*
10 *Association* 2002; 288:(13)1610-21.
- 11 159. Baxter AJ, Beck B, and Phillips K. A randomized prospective trial of
12 rigid and flexible hysteroscopy in an outpatient setting.
13 *Gynaecological Endoscopy* 2002; 11:(6)357-64.
- 14 160. Anastasiadis PG, Koutlaki NG, Skaphida PG *et al.* Endometrial
15 polyps: Prevalence, detection, and malignant potential in women with
16 abnormal uterine bleeding. *European Journal of Gynaecological*
17 *Oncology* 2000; 21:(2)180-3.
- 18 161. Arslan M, Erdem A, Erdem M *et al.* Transvaginal color Doppler
19 ultrasonography for prediction of pre-cancerous endometrial lesions.
20 *International Journal of Gynaecology and Obstetrics* 2003; 80:(3)299-
21 306.
- 22 162. Badawy A, Ash A, Nagele F *et al.* Ultrasonography, hysteroscopy or
23 both? *Journal of Obstetrics and Gynaecology* 1996; 16:(6)551-5.
- 24 163. Ben-Yehuda OM, Kim YB, and Leuchter RS. Does hysteroscopy
25 improve upon the sensitivity of dilatation and curettage in the
26 diagnosis of endometrial hyperplasia or carcinoma? *Gynecologic*
27 *Oncology* 1998; Vol. 68:(1)4-7.
- 28 164. Bernard JP, Lecuru F, Darles C *et al.* Saline contrast
29 sonohysterography as first-line investigation for women with uterine
30 bleeding. *Ultrasound in Obstetrics and Gynecology* 1997; 10:(2)121-
31 5.
- 32 165. Breitkopf DM, Frederickson RA, and Snyder RR. Detection of benign
33 endometrial masses by endometrial stripe measurement in
34 premenopausal women. *Obstetrics and Gynecology* 2004;
35 104:(1)120-5.
- 36 166. Chittachoen A, Theppisai U, Linasmita V *et al.* Sonohysterography
37 in the diagnosis of abnormal uterine bleeding. *Journal of Obstetrics*
38 *and Gynaecology Research* 2000; 26:(4)277-81.
- 39 167. De CL, Kuhn R, and McGinnes D. Saline infusion
40 sonohysterosalpingography, an underutilized technique. *Australian*

- 1 *and New Zealand Journal of Obstetrics and Gynaecology* 1997;
2 37:(2)206-9.
- 3 168. De Vries LD, Dijkhuizen FP, Mol BW *et al.* Comparison of
4 transvaginal sonography, saline infusion sonography, and
5 hysteroscopy in premenopausal women with abnormal uterine
6 bleeding. *Journal of Clinical Ultrasound* 2000; 28:(5)217-23.
- 7 169. Dijkhuizen FP, Brolmann HA, Potters AE *et al.* The accuracy of
8 transvaginal ultrasonography in the diagnosis of endometrial
9 abnormalities. *Obstetrics and Gynecology* 1996; 87:(3)345-9.
- 10 170. Dijkhuizen FP, De Vries LD, Mol BW *et al.* Comparison of
11 transvaginal ultrasonography and saline infusion sonography for the
12 detection of intracavitary abnormalities in premenopausal women.
13 *Ultrasound in Obstetrics and Gynecology* 2000; 15:(5)372-6.
- 14 171. Dueholm M, Forman A, Jensen ML *et al.* Transvaginal sonography
15 combined with saline contrast sonohysterography in evaluating the
16 uterine cavity in premenopausal patients with abnormal uterine
17 bleeding. *Ultrasound in Obstetrics and Gynecology* 2001; 18:(1)54-
18 61.
- 19 172. Dueholm M, Jensen ML, Laursen H *et al.* Can the endometrial
20 thickness as measured by trans-vaginal sonography be used to
21 exclude polyps or hyperplasia in pre-menopausal patients with
22 abnormal uterine bleeding? *Acta Obstetrica et Gynecologica*
23 *Scandinavica* 2001; 80:(7)645-51.
- 24 173. Emanuel MH, Wamsteker K, and Lammes FB. Is dilatation and
25 curettage obsolete for diagnosing intrauterine disorders in
26 premenopausal patients with persistent abnormal uterine bleeding?
27 *Acta Obstetrica et Gynecologica Scandinavica* 1997; 76:(1)65-8.
- 28 174. Emanuel MH, Verdel MJ, Wamsteker K *et al.* A prospective
29 comparison of transvaginal ultrasonography and diagnostic
30 hysteroscopy in the evaluation of patients with abnormal uterine
31 bleeding: clinical implications. *American Journal of Obstetrics and*
32 *Gynecology* 1995; 172:(2 Pt 1)547-52.
- 33 175. Fedele L, Bianchi S, Dorta M *et al.* Transvaginal ultrasonography
34 versus hysteroscopy in the diagnosis of uterine submucous myomas.
35 *Obstetrics and Gynecology* 1991; 77:(5)745-8.
- 36 176. Fothergill DJ, Brown VA, and Hill AS. Histological sampling of the
37 endometrium--a comparison between formal curettage and the
38 Pipelle sampler. *British Journal of Obstetrics & Gynaecology* 1992;
39 99:(9)779-80.
- 40 177. Fukuda M, Shimizu T, Fukuda K *et al.* Transvaginal
41 hysterosonography for differential diagnosis between submucous and

- 1 intramural myoma. *Gynecologic and Obstetric Investigation* 1993;
2 35:(4)236-9.
- 3 178. Garuti G, Sambruni I, Colonnelli M *et al.* Accuracy of hysteroscopy in
4 predicting histopathology of endometrium in 1500 women. *Journal of*
5 *the American Association of Gynecologic Laparoscopists* 2001;
6 8:(2)207-13.
- 7 179. Goldstein SR, Zeltser I, Horan CK *et al.* Ultrasonography-based
8 triage for perimenopausal patients with abnormal uterine bleeding.
9 *American Journal of Obstetrics and Gynecology* 1997; 177:(1)102-8.
- 10 180. Guven MA, Bese T, and Demirkiran F. Comparison of
11 hydrososonography and transvaginal ultrasonography in the detection
12 of intracavitary pathologies in women with abnormal uterine bleeding.
13 *International Journal of Gynecological Cancer* 2004; 14:(1)57-63.
- 14 181. Harmanli OH, Bevilacqua SA, Dandolu V *et al.* Adenomyosis
15 interferes with accurate ultrasonographic detection of uterine
16 leiomyomas. *Archives of Gynecology and Obstetrics* 2005;
17 273:(3)146-9.
- 18 182. Indman PD. Abnormal uterine bleeding. Accuracy of vaginal probe
19 ultrasound in predicting abnormal hysteroscopic findings. *Journal of*
20 *Reproductive Medicine* 1995; 40:(8)545-8.
- 21 183. Kavak Z, Ceyhan N, and Pekin S. Combination of vaginal
22 ultrasonography and pipelle sampling in the diagnosis of endometrial
23 disease. *Australian & New Zealand Journal of Obstetrics &*
24 *Gynaecology*. 1996; 36:(1)63-6.
- 25 184. Kelekci S, Kaya E, Alan M *et al.* Comparison of transvaginal
26 sonography, saline infusion sonography, and office hysteroscopy in
27 reproductive-aged women with or without abnormal uterine bleeding.
28 *Fertility and Sterility* 2005; 84:(3)682-6.
- 29 185. Kent ASH, Haines P, Manners BTB *et al.* Blind endometrial biopsies:
30 Insufficient for diagnosis in women with intrauterine pathology.
31 *Gynaecological Endoscopy* 1998; 7:(5)273-8.
- 32 186. Khanna A, Gupta M, and Shukla RC. Saline perfusion sonography
33 and transvaginal sonography in abnormal uterine bleeding.
34 *Ultrasound International* 2001; 7:(1)31-6.
- 35 187. Koonings PP, Moyer DL, and Grimes DA. A randomized clinical trial
36 comparing Pipelle and Tis-u-trap for endometrial biopsy. *Obstetrics &*
37 *Gynecology* 1990; 75:(2)293-5.
- 38 188. Krampf E, Soby B, and Istre O. How representative are Pipelle
39 endometrial biopsies? A retrospective analysis of 324 biopsies
40 followed by transcervical resection of the endometrium or
41 hysterectomy. *Gynaecological Endoscopy*. 1997; 6:(5)277-81.

189. Kramp E, Bourne T, Hurlen-Solbakken H *et al.* Transvaginal ultrasonography sonohysterography and operative hysteroscopy for the evaluation of abnormal uterine bleeding. *Acta Obstetrica et Gynecologica Scandinavica* 2001; 80:(7)616-22.
190. Laughead MK and Stones LM. Clinical utility of saline solution infusion sonohysterography in a primary care obstetric-gynecologic practice. *American Journal of Obstetrics and Gynecology* 1997; 176:(6)1313-6.
191. Law J. Histological sampling of the endometrium--a comparison between formal curettage and the Pipelle sampler. *British Journal of Obstetrics & Gynaecology* 1993; 100:(5)503-4.
192. Lipscomb GH, Lopatine SM, Stovall TG *et al.* A randomized comparison of the Pipelle, Accurette, and Explora endometrial sampling devices. *American Journal of Obstetrics & Gynecology* 1994; 170:(2)591-4.
193. Litta P, Vasile C, Quintieri F *et al.* Correlation between hysteroscopy and histology in abnormal uterine bleeding. *Italian Journal of Gynaecology and Obstetrics* 1996; 8:(1)22-4.
194. Mancini F, Regnani G, Persico N *et al.* Sonohysterography in the evaluation of endometrial abnormalities. *Italian Journal of Gynaecology and Obstetrics* 2002; 14:(3)69-72.
195. Mathew M, Gupta R, and Krolikowski A. Role of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding. *International Journal of Gynaecology and Obstetrics* 2000; 71:(3)251-3.
196. Mihm LM, Quick VA, Brumfield JA *et al.* The accuracy of endometrial biopsy and saline sonohysterography in the determination of the cause of abnormal uterine bleeding. *American Journal of Obstetrics and Gynecology* 2002; 186:(5)858-60.
197. Nagele F, Bournas N, O'Connor H *et al.* Comparison of carbon dioxide and normal saline for uterine distension in outpatient hysteroscopy. *Fertility and Sterility* 1996; 65:(2)305-9.
198. Nanda S, Chadha N, Sen J *et al.* Transvaginal sonography and saline infusion sonohysterography in the evaluation of abnormal uterine bleeding. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2002; 42:(5)530-4.
199. Ossola MW, Bertulesi C, Iasi L *et al.* Comparison of saline infusion sonography to transvaginal echography and hysteroscopy in the diagnostic evaluation of abnormal uterine bleeding. *Italian Journal of Gynaecology and Obstetrics* 1999; 11:(4)147-52.

- 1 200. Paschopoulos M, Lolis ED, Alamanos Y *et al.* Vaginoscopic
2 hysteroscopy and transvaginal sonography in the evaluation of
3 patients with abnormal uterine bleeding. *Journal of the American*
4 *Association of Gynecologic Laparoscopists* 2001; 8:(4)506-10.
- 5 201. Pascual A, Graupera B, Tresserra F *et al.* Color Doppler transvaginal
6 ultrasound for detecting intrauterine disorders in patients with
7 abnormal uterine bleeding. *Gynaecologia et Perinatologia* 2005;
8 14:(4)157-60.
- 9 202. Pasqualotto EB, Margossian H, Price LL *et al.* Accuracy of
10 preoperative diagnostic tools and outcome of hysteroscopic
11 management of menstrual dysfunction. *Journal of the American*
12 *Association of Gynecologic Laparoscopists* 2000; 7:(2)201-9.
- 13 203. Pasrija S, Trivedi SS, and Narula MK. Prospective study of saline
14 infusion sonohysterography in evaluation of perimenopausal and
15 postmenopausal women with abnormal uterine bleeding. *Journal of*
16 *Obstetrics and Gynaecology Research* 2004; 30:(1)27-33.
- 17 204. Pungetti D, Dimicco R, Mattucci M *et al.* A comparative study
18 between panoramic hysteroscopy and endometrial biopsy. Analysis
19 of 150 cases. *Acta Europaea Fertilitatis* 1990; 21:(4)201-3.
- 20 205. Reinhold C, McCarthy S, Bret PM *et al.* Diffuse adenomyosis:
21 comparison of endovaginal US and MR imaging with histopathologic
22 correlation. *Radiology* 1996; 199:(1)151-8.
- 23 206. Ryu JA, Kim B, Lee J *et al.* Comparison of transvaginal
24 ultrasonography with hysterosonography as a screening method in
25 patients with abnormal uterine bleeding. *Korean Journal of Radiology*
26 2004; 5:(1)39-46.
- 27 207. Saidi MH, Sadler RK, Theis VD *et al.* Comparison of sonography,
28 sonohysterography, and hysteroscopy for evaluation of abnormal
29 uterine bleeding. *Journal of Ultrasound in Medicine* 1997; 16:(9)587-
30 91.
- 31 208. Salim R, Lee C, Davies A *et al.* A comparative study of three-
32 dimensional saline infusion sonohysterography and diagnostic
33 hysteroscopy for the classification of submucous fibroids. *Human*
34 *Reproduction* 2005; 20:(1)253-7.
- 35 209. Scarpellini F, Curto C, Caracussi U *et al.* Transvaginal ultrasound
36 versus histology in endometrial hyperplasia. *Clinical and*
37 *Experimental Obstetrics and Gynecology* 1994; 21:(4)266-9.
- 38 210. Schwarzler P, Concin H, Bosch H *et al.* An evaluation of
39 sonohysterography and diagnostic hysteroscopy for the assessment
40 of intrauterine pathology. *Ultrasound in Obstetrics and Gynecology*
41 1998; 11:(5)337-42.

- 1 211. Smith P, Bakos O, Heimer G *et al.* Transvaginal ultrasound for
2 identifying endometrial abnormality. *Acta Obstetrica et Gynecologica*
3 *Scandinavica* 1991; 70:(7-8)591-4.
- 4 212. Taylor S, Jones S, Dixon A-M *et al.* Evaluation of ultrasound in an
5 outpatient hysteroscopy clinic: Does it alter management in
6 premenopausal women? *Gynaecological Endoscopy* 2001;
7 10:(3)173-8.
- 8 213. Torrejon R, Fernandez-Alba JJ, Carnicer I *et al.* The value of
9 hysteroscopic exploration for abnormal uterine bleeding. *Journal of*
10 *the American Association of Gynecologic Laparoscopists* 1997;
11 4:(4)453-6.
- 12 214. Towbin NA, Gviazda IM, and March CM. Office hysteroscopy versus
13 transvaginal ultrasonography in the evaluation of patients with
14 excessive uterine bleeding. *American Journal of Obstetrics and*
15 *Gynecology* 1996; 174:(6)1678-82.
- 16 215. Widrich T, Bradley LD, Mitchinson AR *et al.* Comparison of saline
17 infusion sonography with office hysteroscopy for the evaluation of the
18 endometrium. *American Journal of Obstetrics and Gynecology* 1996;
19 174:(4)1327-34.
- 20 216. Wood C, Hurley VA, and Leoni M. The value of vaginal ultrasound in
21 the management of menorrhagia. *Australian and New Zealand*
22 *Journal of Obstetrics and Gynaecology* 1993; 33:(2)198-200.
- 23 217. ACOG committee. Von Willebrand's disease in gynecologic practice.
24 *Obstetrics and Gynecology* 2001; 98:(6)1185-6.
- 25 218. Ben-Baruch G, Seidman DS, Schiff E *et al.* Outpatient endometrial
26 sampling with the Pipelle curette. *Gynecologic & Obstetric*
27 *Investigation.* 1994; 37:(4)260-2.
- 28 219. Teale GR and Dunster GD. The Pipelle endometrial suction curette:
29 How useful is it in clinical practice? *Journal of Obstetrics &*
30 *Gynaecology.* 1998; 18:(1)53-5.
- 31 220. Gimpelson RJ and Rappold HO. A comparative study between
32 panoramic hysteroscopy with directed biopsies and dilatation and
33 curettage. A review of 276 cases. *American Journal of Obstetrics and*
34 *Gynecology* 1988; 158:(3 Pt 1)489-92.
- 35 221. Ferry J, Farnsworth A, Webster M *et al.* The efficacy of the pipelle
36 endometrial biopsy in detecting endometrial carcinoma. *Australian &*
37 *New Zealand Journal of Obstetrics & Gynaecology.* 1993; 33:(1)76-8.
- 38 222. Koss LG, Schreiber K, Oberlander SG *et al.* Detection of endometrial
39 carcinoma and hyperplasia in asymptomatic women. *Obstetrics &*
40 *Gynecology* 1984; 64:(1)1-11.

- 1 223. Tahir MM, Bigrigg MA, Browning JJ *et al.* A randomised controlled
2 trial comparing transvaginal ultrasound, outpatient hysteroscopy and
3 endometrial biopsy with inpatient hysteroscopy and curettage. *British*
4 *Journal of Obstetrics and Gynaecology* 1999; 106:(12)1259-64.
- 5 224. Bain C, Parkin DE, and Cooper KG. Is outpatient diagnostic
6 hysteroscopy more useful than endometrial biopsy alone for the
7 investigation of abnormal uterine bleeding in unselected
8 premenopausal women? A randomised comparison. *BJOG: an*
9 *International Journal of Obstetrics and Gynaecology* 2002;
10 109:(7)805-11.
- 11 225. Dijkhuizen FP, Mol BW, Brolmann HA *et al.* The accuracy of
12 endometrial sampling in the diagnosis of patients with endometrial
13 carcinoma and hyperplasia: a meta-analysis. *Cancer* 2000;
14 89:(8)1765-72.
- 15 226. NHS. Toolkit for producing patient information. No. Version 2.0. The
16 Department of Health; 2003.
- 17 227. Kempson E. Informing health consumers. A review of consumer
18 health information needs and services. London: College of Health;
19 1987.
- 20 228. Duman M. Producing patient information. How to research, develop
21 and produce effective information resources. 2nd ed. London: Kings
22 Fund; 2005.
- 23 229. Scriven A and Tucker C. The quality and management of written
24 information presented to women undergoing hysterectomy. *Journal of*
25 *Clinical Nursing* 1997; 6:(2)107-13.
- 26 230. Augustus CE. Beliefs and perceptions of African American women
27 who have had hysterectomy. *Journal of Transcultural Nursing* 2002;
28 13:(4)296-302.
- 29 231. Uskul AK, Ahmad F, Leyland NA *et al.* Women's hysterectomy
30 experiences and decision-making. *Women and Health* 2003;
31 38:(1)53-67.
- 32 232. Webb C. Professional and lay social support for hysterectomy
33 patients. *Journal of Advanced Nursing* 1986; 11:(2)167-77.
- 34 233. Wade J, Pletsch P, and Morgan S. Hysterectomy: what do women
35 need and want to know? *JOGNN - Journal of Obstetric, Gynecologic*
36 *and Neonatal Nursing* 2000; 29:(1)33-42.
- 37 234. Groff JY and Lees E. Decision making, beliefs, and attitudes toward
38 hysterectomy: A focus group study with medically underserved
39 women in Texas. *Journal of Women's Health and Gender-Based*
40 *Medicine* 2000; 9:(Suppl 2)S39-S50.

- 1 235. Skea Z, Harry V, Bhattacharya S *et al.* Women's perceptions of
2 decision-making about hysterectomy. *BJOG: an International Journal*
3 *of Obstetrics and Gynaecology* 2004; 111:(2)133-42.
- 4 236. O'Connor AM, Jacobsen MJ, and Stacey D. An evidence-based
5 approach to managing women's decisional conflict. *JOGNN - Journal*
6 *of Obstetric, Gynecologic, and Neonatal Nursing* 2002; 31:(5)570-81.
- 7 237. Williams RD. A qualitative study of women's hysterectomy
8 experience. *Journal of Women's Health and Gender-Based Medicine*
9 2000; 9:(Suppl 2)S15-S25.
- 10 238. O'Connor AM, Stacey D, Rovner D, Holmes-Rovner M, Tetroe J,
11 Llewellyn-Thomas H, Entwistle V, Rostom A, Fiset V, Barry M, and
12 Jones J. Decision aids for people facing health treatment or
13 screening decisions. (Cochrane Review). In: Cochrane Database of
14 Systematic Reviews, Issue 3, 2002. Oxford: Update Software.
- 15 239. Kennedy AD, Sculpher MJ, Coulter A *et al.* A multicentre randomised
16 controlled trial assessing the costs and benefits of using structured
17 information and analysis of women's preferences in the management
18 of menorrhagia. *Health Technology Assessment* 2003; 7:(8)1-76.
- 19 240. Vuorma S, Rissanen P, Aalto AM *et al.* Impact of patient information
20 booklet on treatment decision - A randomized trial among women
21 with heavy menstruation. *Health Expectations* 2003; 6:(4)290-7.
- 22 241. Vuorma S, Teperi J, Aalto AM *et al.* A randomized trial among women
23 with heavy menstruation -- impact of a decision aid on treatment
24 outcomes and costs. *Health Expectations* 2004; 7:(4)327-37.
- 25 242. Vuorma S, Teperi J, Hurskainen R *et al.* Correlates of women's
26 preferences for treatment of heavy menstrual bleeding. *Patient*
27 *Education and Counseling* 2003; 49:(2)125-32.
- 28 243. Garrud P, Wood M, and Stainsby L. Impact of risk information in a
29 patient education leaflet. *Patient Education and Counseling* 2001;
30 43:(3)301-4.
- 31 244. Ridgeway V and Mathews A. Psychological preparation for surgery: A
32 comparison of methods. *British Journal of Clinical Psychology* 1982;
33 21:(4)271-80.
- 34 245. Cheung LH, Callaghan P, and Chang AM. A controlled trial of
35 psycho-educational interventions in preparing Chinese women for
36 elective hysterectomy. *International Journal of Nursing Studies* 2003;
37 40:(2)207-16.
- 38 246. Cooper KG, Parkin DE, Garratt AM *et al.* Two-year follow up of
39 women randomised to medical management or transcervical
40 resection of the endometrium for heavy menstrual loss: clinical and

- 1 quality of life outcomes. *British Journal of Obstetrics and*
2 *Gynaecology* 1999; 106:(3)258-65.
- 3 247. Bourdrez P, Bongers MY, and Mol BW. Treatment of dysfunctional
4 uterine bleeding: patient preferences for endometrial ablation, a
5 levonorgestrel-releasing intrauterine device, or hysterectomy. *Fertility*
6 *and Sterility* 2004; 82:(1)160-6.
- 7 248. Sculpher MJ, Dwyer N, Browning J *et al.* A survey of women's
8 preferences regarding alternative surgical treatments for
9 menorrhagia. *Health Expectations* 1998; 1:(2)96-105.
- 10 249. Coulter A, Peto V, and Doll H. Patients' preferences and general
11 practitioners' decisions in the treatment of menstrual disorders.
12 *Family Practice* 1994; 11:(1)67-74.
- 13 250. Nevadunsky NS, Bachmann GA, Nosher J *et al.* Women's decision-
14 making determinants in choosing uterine artery embolization for
15 symptomatic fibroids. *Journal of Reproductive Medicine* 2001;
16 46:(10)870-4.
- 17 251. Entwistle VA, Skea ZC, and O'Donnell MT. Decisions about
18 treatment: Interpretations of two measures of control by women
19 having a hysterectomy. *Social Science and Medicine* 2001;
20 53:(6)721-32.
- 21 252. Lindberg CE and Nolan LB. Women's decision making regarding
22 hysterectomy. *JOGNN: Journal of Obstetric, Gynecologic, and*
23 *Neonatal Nursing* 2001; 30:(6)607-16.
- 24 253. Wu S, Chao YY, Yang C *et al.* Decision-making tree for women
25 considering hysterectomy. *Journal of Advanced Nursing* 2005;
26 51:(4)361-8.
- 27 254. Longo MF, Cohen DR, Hood K *et al.* Involving patients in primary
28 care consultations: assessing preferences using discrete choice
29 experiments. *British Journal of General Practice* 2006; 56:(522)35-42.
- 30 255. Entwistle V, Williams B, Skea Z *et al.* Which surgical decisions should
31 patients participate in and how? Reflections on women's recollections
32 of discussions about variants of hysterectomy. *Social Science and*
33 *Medicine* 2006; 62:(2)499-509.
- 34 256. Fry A, Rush R, Busby-Earle C *et al.* Deciding about prophylactic
35 oophorectomy: What is important to women at increased risk of
36 ovarian cancer? *Preventive Medicine: An International Journal*
37 *Devoted to Practice and Theory* 2001; 33:(6)578-85.
- 38 257. Leung PL, Ng PS, Tam WH *et al.* Preference on the treatments for
39 menorrhagia in Hong Kong chinese women. *Gynecologic and*
40 *Obstetric Investigation* 2005; 59:(2)97-101.

- 1 258. Marsh F, Taylor L, Kremer C *et al.* Delivering an effective outpatient
2 service in gynaecology: An assessment of patient preference.
3 *Gynaecological Endoscopy* 2002; 11:(6)337-43.
- 4 259. Coulter A, Entwistle V, and Gilbert D. Sharing decisions with patients:
5 is the information good enough? *British Medical Journal* 1999;
6 318:(7179)318-22.
- 7 260. Lethaby AE, Cooke I, and Rees M. Progesterone/progestogen
8 releasing intrauterine systems for heavy menstrual bleeding.
9 (Cochrane Review). In: Cochrane Database of Systematic Reviews,
10 Issue 4, 2005. Oxford: Update Software.
- 11 261. Stewart A, Cummins C, Gold L *et al.* The effectiveness of the
12 levonorgestrel-releasing intrauterine system in menorrhagia: a
13 systematic review. *BJOG: an International Journal of Obstetrics and*
14 *Gynaecology* 2001; 108:(1)74-86.
- 15 262. Barrington JW, Arunkalaivanan AS, and Abdel-Fattah M. Comparison
16 between the levonorgestrel intrauterine system (LNG-IUS) and
17 thermal balloon ablation in the treatment of menorrhagia. *European*
18 *Journal of Obstetrics, Gynecology, and Reproductive Biology* 2003;
19 108:(1)72-4.
- 20 263. Busfield RA, Farquhar CM, Sowter MC *et al.* A randomised trial
21 comparing the levonorgestrel intrauterine system and thermal balloon
22 ablation for heavy menstrual bleeding. *BJOG: an International*
23 *Journal of Obstetrics and Gynaecology* 2006; 113:(3)257-63.
- 24 264. Cameron IT, Leask R, Kelly RW *et al.* The effects of danazol,
25 mefenamic acid, norethisterone and a progesterone-impregnated coil
26 on endometrial prostaglandin concentrations in women with
27 menorrhagia. *Prostaglandins* 1987; 34:(1)99-110.
- 28 265. Crosignani PG, Vercellini P, Mosconi P *et al.* Levonorgestrel-
29 releasing intrauterine device versus hysteroscopic endometrial
30 resection in the treatment of dysfunctional uterine bleeding.
31 *Obstetrics and Gynecology* 1997; 90:(2)257-63.
- 32 266. Halmesmaki K, Hurskainen R, Tiitinen A *et al.* A randomized
33 controlled trial hysterectomy of levonorgestrel-releasing intrauterine
34 system in the treatment of menorrhagia - Effect of FSH levels and
35 menopausal symptoms. *Human Reproduction* 2004; 19:(2)378-82.
- 36 267. Irvine GA, Campbell-Brown MB, Lumsden MA *et al.* Randomised
37 comparative trial of the levonorgestrel intrauterine system and
38 norethisterone for treatment of idiopathic menorrhagia. *British Journal*
39 *of Obstetrics and Gynaecology* 1998; 105:(6)592-8.

- 1 268. Istre O and Trolle B. Treatment of menorrhagia with the
2 levonorgestrel intrauterine system versus endometrial resection.
3 *Fertility and Sterility* 2001; 76:(2)304-9.
- 4 269. Lahteenmaki P, Haukkamaa M, Puolakka J *et al.* Open randomised
5 study of use of levonorgestrel releasing intrauterine system as
6 alternative to hysterectomy. *British Medical Journal* 1998;
7 316:(7138)1122-6.
- 8 270. Rauramo I, Elo I, and Istre O. Long-term treatment of menorrhagia
9 with levonorgestrel intrauterine system versus endometrial resection.
10 *Obstetrics and Gynecology* 2004; 104:(6)1314-21.
- 11 271. Reid PC and Virtanen-Kari S. Randomised comparative trial of the
12 levonorgestrel intrauterine system and mefenamic acid for the
13 treatment of idiopathic menorrhagia: a multiple analysis using total
14 menstrual fluid loss, menstrual blood loss and pictorial blood loss
15 assessment charts. *BJOG: an International Journal of Obstetrics and*
16 *Gynaecology* 2005; 112:(8)1121-5.
- 17 272. Soysal M, Soysal S, and Ozer S. A randomized controlled trial of
18 levonorgestrel releasing IUD and thermal balloon ablation in the
19 treatment of menorrhagia. *Zentralblatt fur Gynakologie* 2002;
20 124:(4)213-9.
- 21 273. Borgelt-Hansen L. Oral contraceptives: an update on health benefits
22 and risks. *Journal of the American Pharmaceutical Association* 2001;
23 41:(6)875-86.
- 24 274. Iyer V, Farquhar C, and Jepson R. Oral contraceptive pills for heavy
25 menstrual bleeding. (Cochrane Review). In: Cochrane Database of
26 Systematic Reviews, Issue 2, 2000. Oxford: Update Software.
- 27 275. Coulter A, Kelland J, Peto V *et al.* Treating menorrhagia in primary
28 care: An overview of drug trials and a survey of prescribing practice.
29 *International Journal of Technology Assessment in Health Care* 1995;
30 11:(3)456-71.
- 31 276. Fraser IS and McCarron G. Randomized trial of 2 hormonal and 2
32 prostaglandin-inhibiting agents in women with a complaint of
33 menorrhagia. *Australian and New Zealand Journal of Obstetrics and*
34 *Gynaecology* 1991; 31:(1)66-70.
- 35 277. Lethaby A, Irvine G, and Cameron I. Cyclical progestogens for heavy
36 menstrual bleeding. (Cochrane Review). In: Cochrane Database of
37 Systematic Reviews, Issue 4, 2004. Oxford: Update Software.
- 38 278. Bonduelle M, Walker JJ, and Calder AA. A comparative study of
39 danazol and norethisterone in dysfunctional uterine bleeding
40 presenting as menorrhagia. *Postgraduate Medical Journal* 1991;
41 67:(791)833-6.

- 1 279. Dunphy BC, Goerzen J, Greene CA *et al.* A double-blind randomised
2 study comparing danazol and medroxyprogesterone acetate in the
3 management of menorrhagia. *Journal of Obstetrics and Gynaecology*
4 1998; 18:(6)553-5.
- 5 280. Higham JM and Shaw RW. A comparative study of danazol, a
6 regimen of decreasing doses of danazol, and norethindrone in the
7 treatment of objectively proven unexplained menorrhagia. *American*
8 *Journal of Obstetrics and Gynecology* 1993; 169:(5)1134-9.
- 9 281. Preston JT, Cameron IT, Adams EJ *et al.* Comparative study of
10 tranexamic acid and norethisterone in the treatment of ovulatory
11 menorrhagia. *British Journal of Obstetrics and Gynaecology* 1995;
12 102:(5)401-6.
- 13 282. Fraser IS. Treatment of ovulatory and anovulatory dysfunctional
14 uterine bleeding with oral progestogens. *Australian and New Zealand*
15 *Journal of Obstetrics and Gynaecology* 1990; 30:(4)353-6.
- 16 283. Beaumont H, Augood C, Duckitt K, and Lethaby A. Danazol for
17 heavy menstrual bleeding. (Cochrane Review). In: Cochrane
18 Database of Systematic Reviews, Issue 4, 2004. Oxford: Update
19 Software.
- 20 284. Turnbull AC and Rees MC. Gestrinone in the treatment of
21 menorrhagia. *British Journal of Obstetrics and Gynaecology* 1990;
22 97:(8)713-5.
- 23 285. Chimbira TH, Anderson AB, Naish C *et al.* Reduction of menstrual
24 blood loss by danazol in unexplained menorrhagia: lack of effect of
25 placebo. *British Journal of Obstetrics and Gynaecology* 1980;
26 87:(12)1152-8.
- 27 286. Dockeray CJ, Sheppard BL, and Bonnar J. Comparison between
28 mefenamic acid and danazol in the treatment of established
29 menorrhagia. *British Journal of Obstetrics and Gynaecology* 1989;
30 96:(7)840-4.
- 31 287. Lamb MP. Danazol in menorrhagia: A double blind placebo controlled
32 trial. *Journal of Obstetrics and Gynaecology* 1987; 7:(3)212-6.
- 33 288. National Collaborating Centre for Women's and Children's Health.
34 Long acting reversible contraception: the effective and appropriate
35 use of long-acting reversible contraception. 2005. London, RCOG
36 Press.
- 37 289. Task force on long-acting agents for the regulation of fertility.
38 Multinational comparative clinical trial of long-acting injectable
39 contraceptives: norethisterone enanthate given in two dosage
40 regimens and depot-medroxyprogesterone acetate. Final report.
41 *Contraception* 1983; 28:(1)1-20.

- 1 290. Said S, Omar K, Koetsawang S *et al.* A multicentered phase III
2 comparative clinical trial of depot-medroxyprogesterone acetate given
3 three-monthly at doses of 100 mg or 150 mg: II. The comparison of
4 bleeding patterns. *Contraception* 1987; 35:(6)591-610.
- 5 291. Canto De Cetina TE, Canto P, and Ordonez LM. Effect of counseling
6 to improve compliance in Mexican women receiving depot-
7 medroxyprogesterone acetate. *Contraception* 2001; 63:(3)143-6.
- 8 292. Friedman AJ, Hoffman DI, Comite F *et al.* Treatment of leiomyomata
9 uteri with leuprolide acetate depot: a double-blind, placebo-controlled,
10 multicenter study. The Leuprolide Study Group. *Obstetrics and*
11 *Gynecology* 1991; 77:(5)720-5.
- 12 293. Takeuchi H, Kobori H, Kikuchi I *et al.* A prospective randomized study
13 comparing endocrinological and clinical effects of two types of GnRH
14 agonists in cases of uterine leiomyomas or endometriosis. *Journal of*
15 *Obstetrics and Gynaecology Research* 2000; 26:(5)325-31.
- 16 294. Carr BR, Marshburn PB, Weatherall PT *et al.* An evaluation of the
17 effect of gonadotropin-releasing hormone analogs and
18 medroxyprogesterone acetate on uterine leiomyomata volume by
19 magnetic resonance imaging: a prospective, randomized, double
20 blind, placebo-controlled, crossover trial. *Journal of Clinical*
21 *Endocrinology and Metabolism* 1993; 76:(5)1217-23.
- 22 295. Friedman AJ, Barbieri RL, Doubilet PM *et al.* A randomized, double-
23 blind trial of a gonadotropin-releasing hormone agonist (leuprolide)
24 with or without medroxyprogesterone acetate in the treatment of
25 leiomyomata uteri. *Obstetrical and Gynecological Survey* 1988;
26 43:(8)484-5.
- 27 296. Friedman AJ, Daly M, Juneau-Norcross M *et al.* A prospective,
28 randomized trial of gonadotropin-releasing hormone agonist plus
29 estrogen-progestin or progestin 'add-back' regimens for women with
30 leiomyomata uteri. *Journal of Clinical Endocrinology and Metabolism*
31 1993; 76:(6)1439-45.
- 32 297. Nakayama H, Yano T, Sagara Y *et al.* Estriol add-back therapy in the
33 long-acting gonadotropin-releasing hormone agonist treatment of
34 uterine leiomyomata. *Gynecological Endocrinology* 1999; 13:(6)382-
35 9.
- 36 298. Palomba S, Affinito P, Tommaselli GA *et al.* A clinical trial of the
37 effects of tibolone administered with gonadotropin-releasing hormone
38 analogues for the treatment of uterine leiomyomata. *Fertility and*
39 *Sterility* 1998; 70:(1)111-8.
- 40 299. Palomba S, Orio F, Jr., Morelli M *et al.* Raloxifene administration in
41 women treated with gonadotropin-releasing hormone agonist for

- 1 uterine leiomyomas: effects on bone metabolism. *Journal of Clinical*
2 *Endocrinology and Metabolism* 2002; 87:(10)4476-81.
- 3 300. Palomba S, Orio F, Jr., Russo T *et al.* Gonadotropin-releasing
4 hormone agonist with or without raloxifene: effects on cognition,
5 mood, and quality of life. *Fertility and Sterility* 2004; 82:(2)480-2.
- 6 301. Schlaff WD, Zerhouni EA, Huth JA *et al.* A placebo-controlled trial of
7 a depot gonadotropin-releasing hormone analogue (leuprolide) in the
8 treatment of uterine leiomyomata. *Obstetrics and Gynecology* 1989;
9 74:(6)856-62.
- 10 302. Lethaby A, Farquhar C, and Cooke I. Antifibrinolytics for heavy
11 menstrual bleeding. (Cochrane Review). In: Cochrane Database of
12 Systematic Reviews, Issue 4, 2004. Oxford: Update Software.
- 13 303. Wellington K and Wagstaff AJ. Tranexamic acid: a review of its use in
14 the management of menorrhagia. *Drugs* 2003; 63:(13)1417-33.
- 15 304. Nilsson L and Rybo G. Treatment of menorrhagia with an
16 antifibrinolytic agent, tranexamic acid (AMCA). *Acta Obstetricia et*
17 *Gynecologica Scandinavica* 1967; 46:572-80.
- 18 305. Edlund M, Andersson K, Rybo G *et al.* Reduction of menstrual blood
19 loss in women suffering from idiopathic menorrhagia with a novel
20 antifibrinolytic drug (Kabi 2161). *British Journal of Obstetrics and*
21 *Gynaecology* 1995; 102:(11)913-7.
- 22 306. Callender ST, Warner GT, and Cope E. Treatment of menorrhagia
23 with tranexamic acid. A double-blind trial. *British Medical Journal*
24 1970; 4:(729)214-6.
- 25 307. Bonnar J and Sheppard BL. Treatment of menorrhagia during
26 menstruation: randomised controlled trial of ethamsylate, mefenamic
27 acid, and tranexamic acid. *British Medical Journal* 1996;
28 313:(7057)579-82.
- 29 308. Andersch B, Milsom I, and Rybo G. An objective evaluation of
30 flurbiprofen and tranexamic acid in the treatment of idiopathic
31 menorrhagia. *Acta Obstetricia et Gynecologica Scandinavica* 1988;
32 67:(7)645-8.
- 33 309. Vermeylen J, Verhaegen-Declercq ML, Verstraete M *et al.* A double
34 blind study of the effect of tranexamic acid in essential menorrhagia.
35 *Thrombosis et Diathesis Haemorrhagica* 1968; 20:(3)583-7.
- 36 310. Lethaby A, Augood C, and Duckitt K. Nonsteroidal anti-inflammatory
37 drugs for heavy menstrual bleeding. (Cochrane Review). In:
38 Cochrane Database of Systematic Reviews, Issue 3, 2004. Oxford:
39 Update Software.

- 1 311. Cameron IT, Haining R, Lumsden MA *et al.* The effects of mefenamic
2 acid and norethisterone on measured menstrual blood loss.
3 *Obstetrics and Gynecology* 1990; 76:(1)85-8.
- 4 312. Chamberlain G, Freeman R, Price F *et al.* A comparative study of
5 ethamsylate and mefenamic acid in dysfunctional uterine bleeding.
6 *British Journal of Obstetrics and Gynaecology* 1991; 98:(7)707-11.
- 7 313. Creatsas G, Cardamakis E, Deligeoroglou E *et al.* Tenoxicam versus
8 lynestrenol-ethinyl estradiol treatment of dysfunctional uterine
9 bleeding cases during adolescence. *Journal of Pediatric and*
10 *Adolescent Gynecology* 1998; 11:(4)177-80.
- 11 314. Fraser IS, Pearse C, Shearman RP *et al.* Efficacy of mefenamic acid
12 in patients with a complaint of menorrhagia. *Obstetrics and*
13 *Gynecology* 1981; 58:(5)543-51.
- 14 315. Grover V, Usha R, Gupta U *et al.* Management of cyclical
15 menorrhagia with prostaglandin synthetase inhibitor. *Asia-Oceania*
16 *Journal of Obstetrics and Gynaecology* 1990; 16:(3)255-9.
- 17 316. Hall P, Maclachlan N, Thorn N *et al.* Control of menorrhagia by the
18 cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid.
19 *British Journal of Obstetrics and Gynaecology* 1987; 94:(6)554-8.
- 20 317. Jakubowicz DL and Wood C. The use of the prostaglandin
21 synthetase inhibitor mefenamic acid in the treatment of menorrhagia.
22 *Australian & New Zealand Journal of Obstetrics & Gynaecology* 1978;
23 18:(2)135-8.
- 24 318. van Eijkeren MA, Christiaens GC, Geuze HJ *et al.* Effects of
25 mefenamic acid on menstrual hemostasis in essential menorrhagia.
26 *American Journal of Obstetrics and Gynecology* 1992; 166:(5)1419-
27 28.
- 28 319. Vargyas JM, Campeau JD, and Mishell DR, Jr. Treatment of
29 menorrhagia with meclofenamate sodium. *American Journal of*
30 *Obstetrics and Gynecology* 1987; 157:(4 Pt 1)944-50.
- 31 320. Ylikorkala O and Pekonen F. Naproxen reduces idiopathic but not
32 fibromyoma-induced menorrhagia. *Obstetrics and Gynecology* 1986;
33 68:(1)10-2.
- 34 321. Harrison RF and Cambell S. A double-blind trial of ethamsylate in the
35 treatment of primary and intrauterine-device menorrhagia. *Lancet*
36 1976; 2:(7980)283-5.
- 37 322. Faculty of Family Planning and Reproductive Health Care CEU.
38 FFPRHC Guidance (October 2003): First prescription of combined
39 oral contraception.[erratum appears in J Fam Plann Reprod Health
40 Care. 2004 Jan;30(1):63]. *Journal of Family Planning and*
41 *Reproductive Health Care* 2003; 29:(4)209-22.

- 1 323. Faculty of Family Planning and Reproductive Health Care CEU.
2 FFPRHC Guidance (October 2003): First prescription of combined
3 oral contraception.[erratum appears in J Fam Plann Reprod Health
4 Care. 2004 Jan;30(1):63]. *Journal of Family Planning and*
5 *Reproductive Health Care* 2003; 29:(4)209-22.
- 6 324. Makarainen L and Ylikorkala O. Menstrual blood loss in
7 dysmenorrhoea: effects of proquazone and indomethacin. *British*
8 *Journal of Obstetrics and Gynaecology* 1983; 90:(6)570-2.
- 9 325. Ingemanson CA, Sikstrom B, Rybo G *et al.* Double-BLIND,
10 PLACEBO-CONTROLled evaluation of diclofenac in the management
11 of patients with IUD-related menorrhagia. *ADV THER* 1991; 8:(6)287-
12 92.
- 13 326. Chimbira TH, Cope E, Anderson AB *et al.* The effect of danazol on
14 menorrhagia, coagulation mechanisms, haematological indices and
15 body weight. *British Journal of Obstetrics and Gynaecology* 1979;
16 86:(1)46-50.
- 17 327. Need JA, Forbes KL, Milazzo L *et al.* Danazol in the treatment of
18 menorrhagia: The effect of a 1 month induction dose (200 mg) and 2
19 month's maintenance therapy (200 mg, 100 mg, 50 mg or placebo).
20 *Australian and New Zealand Journal of Obstetrics and Gynaecology*
21 1992; 32:(4)346-52.
- 22 328. Milsom I, Andersson K, Andersch B *et al.* A comparison of
23 flurbiprofen, tranexamic acid, and a levonorgestrel-releasing
24 intrauterine contraceptive device in the treatment of idiopathic
25 menorrhagia. *American Journal of Obstetrics and Gynecology* 1991;
26 164:(3)879-83.
- 27 329. Bongers MY, Mol BWJ, and Brolmann HAM. Prognostic factors for
28 the success of thermal balloon ablation in the treatment of
29 menorrhagia. *Obstetrics and Gynecology* 2002; 99:(6)1060-6.
- 30 330. Marjoribanks J, Lethaby A, and Farquhar C. Surgery versus medical
31 therapy for heavy menstrual bleeding. (Cochrane Review). In:
32 Cochrane Database of Systematic Reviews, Issue 2, 2006. Oxford:
33 Update Software.
- 34 331. Kuppermann M, Varner RE, Summitt RL, Jr. *et al.* Effect of
35 hysterectomy vs medical treatment on health-related quality of life
36 and sexual functioning: the medicine or surgery (Ms) randomized
37 trial. *JAMA: the journal of the American Medical Association* 2004;
38 291:(12)1447-55.
- 39 332. Istre O and Kittelsen N. A randomised study comparing
40 levonorgestrel intra-uterine system (LNG IUS) and TCRE in the
41 treatment of menorrhagia. *Gynaecological Endoscopy* 1997;
42 6:(Supplement 2)42.

- 1 333. Johnson N, Busfield R, Sadler L *et al.* The management of
2 menorrhagia--SMART study (Satisfaction with Mirena and Ablation: a
3 Randomised Trial). *BJOG: an International Journal of Obstetrics and*
4 *Gynaecology* 2001; 108:(7)773-4.
- 5 334. Haynes PJ, Hodgson H, Anderson AB *et al.* Measurement of
6 menstrual blood loss in patients complaining of menorrhagia. *British*
7 *Journal of Obstetrics and Gynaecology* 1977; 84:(10)763-8.
- 8 335. Lethaby A, Shepperd S, Cooke I, and Farquhar C. Endometrial
9 resection and ablation versus hysterectomy for heavy menstrual
10 bleeding. (Cochrane Review). In: Cochrane Database of Systematic
11 Reviews, Issue 2, 2004. Oxford: Update Software.
- 12 336. Aberdeen Endometrial Ablation Trials Group. A randomised trial of
13 endometrial ablation versus hysterectomy for the treatment of
14 dysfunctional uterine bleeding: outcome at four years. [erratum
15 appears in Br J Obstet Gynaecol. 1999 Aug;106(8):876; PMID:
16 10453847]. *British Journal of Obstetrics and Gynaecology* 1999;
17 106:(4)360-6.
- 18 337. Shawki O, Hebert AS, and Peters AJ. Endometrial preparation before
19 hysteroscopic surgery for uterine bleeding: A prospective randomized
20 multicenter evaluation. *Middle East Fertility Society Journal* 2000;
21 5:(1)48-52.
- 22 338. Zupi E, Zullo F, Marconi D *et al.* Hysteroscopic endometrial resection
23 versus laparoscopic supracervical hysterectomy for menorrhagia: a
24 prospective randomized trial. *American Journal of Obstetrics and*
25 *Gynecology* 2003; 188:(1)7-12.
- 26 339. Garside R, Stein K, Wyatt K *et al.* The effectiveness and cost-
27 effectiveness of microwave and thermal balloon endometrial ablation
28 for heavy menstrual bleeding: a systematic review and economic
29 modelling. *Health Technology Assessment* 2004; 8:(3)iii-155.
- 30 340. Lethaby A and Hickey M. Endometrial destruction techniques for
31 heavy menstrual bleeding. (Cochrane Review). In: Cochrane
32 Database of Systematic Reviews, Issue Oxford, 2005. Oxford:
33 Update Software.
- 34 341. Bongers MY, Bourdrez P, Heintz APM *et al.* Bipolar radio frequency
35 endometrial ablation compared with balloon endometrial ablation in
36 dysfunctional uterine bleeding: Impact on patients' health-related
37 quality of life. *Fertility and Sterility* 2005; 83:(3)724-34.
- 38 342. Abbott J, Hawe J, Hunter D *et al.* A double-blind randomized trial
39 comparing the Cavaterm and the NovaSure endometrial ablation
40 systems for the treatment of dysfunctional uterine bleeding. *Fertility*
41 *and Sterility* 2003; 80:(1)203-8.

- 1 343. Bhattacharya S, Cameron IM, Parkin DE *et al.* A pragmatic
2 randomised comparison of transcervical resection of the
3 endometrium with endometrial laser ablation for the treatment of
4 menorrhagia. *British Journal of Obstetrics and Gynaecology* 1997;
5 104:(5)601-7.
- 6 344. Boujida VH, Philipsen T, Pelle J *et al.* Five-year follow-up of
7 endometrial ablation: endometrial coagulation versus endometrial
8 resection. *Obstetrics and Gynecology* 2002; 99:(6)988-92.
- 9 345. Cooper KG, Bain C, Lawrie L *et al.* A randomised comparison of
10 microwave endometrial ablation with transcervical resection of the
11 endometrium; follow up at a minimum of five years. *BJOG: an*
12 *International Journal of Obstetrics and Gynaecology* 2005;
13 112:(4)470-5.
- 14 346. Cooper J, Gimpelson R, Laberge P *et al.* A randomized, multicenter
15 trial of safety and efficacy of the novasure system in the treatment of
16 menorrhagia. *Journal of the American Association of Gynecologic*
17 *Laparoscopists* 2002; 9:(4)418-28.
- 18 347. Cooper JM, Anderson TL, Fortin CA *et al.* Microwave endometrial
19 ablation vs. rollerball electroablation for menorrhagia: A multicenter
20 randomized trial. *Journal of the American Association of Gynecologic*
21 *Laparoscopists* 2004; 11:(3)394-403.
- 22 348. Corson SL, Brill AI, Brooks PG *et al.* One-year results of the Vesta
23 system for endometrial ablation. *Journal of the American Association*
24 *of Gynecologic Laparoscopists* 2000; 7:(4)489-97.
- 25 349. Corson SL. A multicenter evaluation of endometrial ablation by Hydro
26 ThermAblator and rollerball for treatment of menorrhagia. *Journal of*
27 *the American Association of Gynecologic Laparoscopists* 2001;
28 8:(3)359-67.
- 29 350. Duleba AJ, Heppard MC, Soderstrom RM *et al.* A randomized study
30 comparing endometrial cryoablation and rollerball electroablation for
31 treatment of dysfunctional uterine bleeding. *Journal of the American*
32 *Association of Gynecologic Laparoscopists* 2003; 10:(1)17-26.
- 33 351. McClure N, Mamers PM, Healy DL *et al.* A quantitative assessment of
34 endometrial electrocautery in the management of menorrhagia and a
35 comparative report of argon laser endometrial ablation.
36 *Gynaecological Endoscopy* 1992; 1:(4)-202.
- 37 352. Perino A, Castelli A, Cucinella G *et al.* A randomized comparison of
38 endometrial laser intrauterine thermotherapy and hysteroscopic
39 endometrial resection. *Fertility and Sterility* 2004; 82:(3)731-4.

- 1 353. Soysal ME, Soysal SK, and Vicdan K. Thermal balloon ablation in
2 myoma-induced menorrhagia under local anesthesia. *Gynecologic*
3 *and Obstetric Investigation* 2001; 51:(2)128-33.
- 4 354. Vercellini P, Oldani S, Yaylayan L *et al.* Randomized comparison of
5 vaporizing electrode and cutting loop for endometrial ablation.
6 *Obstetrics and Gynecology* 1999; 94:(4)521-7.
- 7 355. Van Zon-Rabelink IA, Vleugels MP, Merkus HM *et al.* Endometrial
8 ablation by rollerball electrocoagulation compared to uterine balloon
9 thermal ablation. Technical and safety aspects. *European Journal of*
10 *Obstetrics, Gynecology, and Reproductive Biology* 2003; 110:(2)220-
11 3.
- 12 356. Van Zon-Rabelink IA, Vleugels MP, Merkus HM *et al.* Efficacy and
13 satisfaction rate comparing endometrial ablation by rollerball
14 electrocoagulation to uterine balloon thermal ablation in a randomised
15 controlled trial. *European Journal of Obstetrics, Gynecology, and*
16 *Reproductive Biology* 2004; 114:(1)97-103.
- 17 357. Loffer FD. Three-year comparison of thermal balloon and rollerball
18 ablation in treatment of menorrhagia. *Journal of the American*
19 *Association of Gynecologic Laparoscopists* 2001; 8:(1)48-54.
- 20 358. Loffer FD and Grainger D. Five-year follow-up of patients participating
21 in a randomized trial of uterine balloon therapy versus rollerball
22 ablation for treatment of menorrhagia. *Journal of the American*
23 *Association of Gynecologic Laparoscopists* 2002; 9:(4)429-35.
- 24 359. Grainger DA, Tjaden BL, Rowland C *et al.* Thermal balloon and
25 rollerball ablation to treat menorrhagia: Two-year results of a
26 multicenter, prospective, randomized, clinical trial. *Journal of the*
27 *American Association of Gynecologic Laparoscopists* 2000; 7:(2)175-
28 9.
- 29 360. Meyer WR, Walsh BW, Grainger DA *et al.* Thermal balloon and
30 rollerball ablation to treat menorrhagia: a multicenter comparison.
31 *Obstetrics and Gynecology* 1998; 92:(1)98-103.
- 32 361. Bongers MY, Bourdrez P, Mol BWJ *et al.* Randomised controlled trial
33 of bipolar radio-frequency endometrial ablation and balloon
34 endometrial ablation. *BJOG: an International Journal of Obstetrics*
35 *and Gynaecology* 2004; 111:(10)1095-102.
- 36 362. Goldrath MH. Evaluation of HydroThermAblator and Rollerball
37 Endometrial Ablation for Menorrhagia 3 Years after Treatment.
38 *Journal of the American Association of Gynecologic Laparoscopists*
39 2003; 10:(4)505-11.
- 40 363. Pellicano M, Guida M, Acunzo G *et al.* Hysteroscopic transcervical
41 endometrial resection versus thermal destruction for menorrhagia: A

- 1 prospective randomized trial on satisfaction rate. *American Journal of*
2 *Obstetrics and Gynecology* 2002; 187:(3)545-50.
- 3 364. Vihko KK, Raitala R, and Taina E. Endometrial thermoablation for
4 treatment of menorrhagia: comparison of two methods in outpatient
5 setting. *Acta Obstetrica et Gynecologica Scandinavica* 2003;
6 82:(3)269-74.
- 7 365. Bhattacharya S, Mollison J, Pinion S *et al.* A comparison of bladder
8 and ovarian function two years following hysterectomy or endometrial
9 ablation. *British Journal of Obstetrics and Gynaecology* 1996;
10 103:(9)898-903.
- 11 366. Bongers MY, Mol BW, Dijkhuizen FP *et al.* Is balloon ablation as
12 effective as endometrial electroresection in the treatment of
13 menorrhagia? *Journal of Laparoendoscopic and Advanced Surgical*
14 *Techniques-Part A* 2000; 10:(2)85-92.
- 15 367. Gervaise A, Fernandez H, Capella-Allouc S *et al.* Thermal balloon
16 ablation versus endometrial resection for the treatment of abnormal
17 uterine bleeding. *Human Reproduction* 1999; 14:(11)2743-7.
- 18 368. Mousa HA, bou El Senoun GMS, and Mahmood TA. Medium-term
19 clinical outcome of women with menorrhagia treated by rollerball
20 endometrial ablation versus abdominal hysterectomy with
21 conservation of at least one ovary. *Acta Obstetrica et Gynecologica*
22 *Scandinavica* 2001; 80:(5)442-6.
- 23 369. Clarke A, Judge A, Herbert A *et al.* Readmission to hospital 5 years
24 after hysterectomy or endometrial resection in a national cohort
25 study. *Quality and Safety in Health Care* 2005; 14:(1)41-7.
- 26 370. Dequesne JH, Gallinat A, Garza-Leal JG *et al.* Thermoregulated
27 radiofrequency endometrial ablation. *International Journal of Fertility*
28 *and Womens Medicine* 1997; 42:(5)311-8.
- 29 371. Donnez J, Polet R, Rabinovitz R *et al.* Endometrial laser intrauterine
30 thermotherapy: The first series of 100 patients observed for 1 year.
31 *Fertility and Sterility* 2000; 74:(4)791-6.
- 32 372. Dutton C, Ackerson L, and Phelps-Sandall B. Outcomes after
33 rollerball endometrial ablation for menorrhagia. *Obstetrics and*
34 *Gynecology* 2001; 98:(1)35-9.
- 35 373. El-Toukhy T, Chandakas S, Grigoriadis T *et al.* Outcome of the first
36 220 cases of endometrial balloon ablation using Cavaterm plus.
37 *Journal of Obstetrics and Gynaecology* 2004; 24:(6)680-3.
- 38 374. Erian J. Endometrial ablation in the treatment of menorrhagia. *British*
39 *Journal of Obstetrics and Gynaecology* 1994; 101:(Suppl 11)19-22.

- 1 375. Erian MM and Goh JT. Transcervical endometrial resection. *Journal*
2 *of the American Association of Gynecologic Laparoscopists* 1996;
3 3:(2)263-6.
- 4 376. Feitoza SS, Gebhart JB, Gostout BS *et al.* Efficacy of thermal balloon
5 ablation in patients with abnormal uterine bleeding. *American Journal*
6 *of Obstetrics and Gynecology* 2003; 189:(2)453-7.
- 7 377. Ferry J and Rankin L. Transcervical resection of the endometrium
8 using intracervical block only. A review of 278 procedures. *Australian*
9 *and New Zealand Journal of Obstetrics and Gynaecology* 1994;
10 34:(4)457-61.
- 11 378. Friberg B and Ahlgren M. Thermal balloon endometrial destruction:
12 The outcome of treatment of 117 women followed up for a maximum
13 period of 4 years. *Gynaecological Endoscopy* 2000; 9:(6)389-95.
- 14 379. Gallinat A and Cosgriff N. Endometrial ablation by electroballoon
15 coagulation: Long-term results. *Gynaecological Endoscopy* 2001;
16 10:(1)37-43.
- 17 380. Gallinat A. NovaSure impedance controlled system for endometrial
18 ablation: Three-year follow-up on 107 patients. *American Journal of*
19 *Obstetrics and Gynecology* 2004; 191:(5)1585-9.
- 20 381. Gandhi SV, Fear KBC, and Sturdee DW. Endometrial resection:
21 Factors affecting long-term success. *Gynaecological Endoscopy*
22 1999; 8:(1)41-50.
- 23 382. Garry R, Erian J, and Grochmal SA. A multi-centre collaborative
24 study into the treatment of menorrhagia by Nd-YAG laser ablation of
25 the endometrium. *British Journal of Obstetrics and Gynaecology*
26 1991; 98:(4)357-62.
- 27 383. Garry R, Shelley-Jones D, Mooney P *et al.* Six hundred endometrial
28 laser ablations. *Obstetrics and Gynecology* 1995; 85:(1)24-9.
- 29 384. Lefler HT, Jr. Long-term follow-up of endometrial ablation by modified
30 loop resection. *Journal of the American Association of Gynecologic*
31 *Laparoscopists* 2003; 10:(4)517-20.
- 32 385. McPherson K, Herbert A, Judge A *et al.* Psychosexual health 5 years
33 after hysterectomy: Population-based comparison with endometrial
34 ablation for dysfunctional uterine bleeding. *Health Expectations* 2005;
35 8:(3)234-43.
- 36 386. McPherson K, Herbert A, Judge A *et al.* Self-reported bladder
37 function five years post-hysterectomy. *Journal of Obstetrics and*
38 *Gynaecology* 2005; 25:(5)469-75.

- 1 387. O'Connor H and Magos A. Endometrial resection for the treatment of
2 menorrhagia. *The New England journal of medicine* 1996;
3 335:(3)151-6.
- 4 388. Parkin DE. Microwave endometrial ablation (MEA): A safe technique?
5 Complication data from a prospective series of 1400 cases.
6 *Gynaecological Endoscopy* 2000; 9:(6)385-8.
- 7 389. Perez-Medina T, Haya J, San FL *et al*. Factors influencing long-term
8 outcome of loop endometrial resection. *Journal of the American*
9 *Association of Gynecologic Laparoscopists* 2002; 9:(3)272-6.
- 10 390. Pooley AS, Ewen SP, and Sutton CJG. Does transcervical resection
11 of the endometrium for menorrhagia really avoid hysterectomy? Life
12 table analysis of a large series. *Journal of the American Association*
13 *of Gynecologic Laparoscopists* 1998; 5:(3)229-35.
- 14 391. Quenby S. Listening to the patient: endometrial resection. (Research
15 into patients' views in Liverpool.). *Br J Hospital Medicine* 1997;
16 57:(10)508-11.
- 17 392. Roushdy M, Farag O, Momtaz M *et al*. The relation between uterine
18 volume and the success of endometrial resection in menorrhagia.
19 *Middle East Fertility Society Journal* 1996; 1:(2)142-5.
- 20 393. Seidman DS, Bitman G, Mashiach S *et al*. The effect of increasing
21 age on the outcome of hysteroscopic endometrial resection for
22 management of dysfunctional uterine bleeding. *Journal of the*
23 *American Association of Gynecologic Laparoscopists* 2000; 7:(1)115-
24 9.
- 25 394. Sharma B, Preston J, and Ray C. Microwave endometrial ablation for
26 menorrhagia: Outcome at 2 years - Experience of a district general
27 hospital. *Journal of Obstetrics and Gynaecology* 2004; 24:(8)916-9.
- 28 395. Steffensen AJ and Schuster M. Endometrial resection and late
29 reoperation in the treatment of menorrhagia. *Journal of the American*
30 *Association of Gynecologic Laparoscopists* 1997; 4:(3)325-9.
- 31 396. Thijssen RF. Radiofrequency induced endometrial ablation: an
32 update. *British Journal of Obstetrics and Gynaecology* 1997;
33 104:(5)608-13.
- 34 397. Tsaltas J, Taylor N, and Healey M. A 6-year review of the outcome of
35 endometrial ablation. *Australian and New Zealand Journal of*
36 *Obstetrics and Gynaecology* 1998; 38:(1)69-72.
- 37 398. Vilos GA, Fortin CA, Sanders B *et al*. Clinical trial of the uterine
38 thermal balloon for treatment of menorrhagia. *Journal of the*
39 *American Association of Gynecologic Laparoscopists* 1997; 4:(5)559-
40 65.

- 1 399. Vilos GA, Vilos EC, and King JH. Experience with 800 hysteroscopic
2 endometrial ablations. *Journal of the American Association of*
3 *Gynecologic Laparoscopists* 1996; 4:(1)33-8.
- 4 400. Wright B, Gannon MJ, Greenberg M *et al.* Psychiatric morbidity
5 following endometrial ablation and its association with genuine
6 menorrhagia. *BJOG: an International Journal of Obstetrics and*
7 *Gynaecology* 2003; 110:(4)358-63.
- 8 401. Sowter MC, Lethaby A, and Singla AA. Pre-operative endometrial
9 thinning agents before endometrial destruction for heavy menstrual
10 bleeding. (Cochrane Review). In: Cochrane Database of Systematic
11 Reviews, Issue 3, 2004. Oxford: Update Software.
- 12 402. English J, Daly S, McGuinness N *et al.* Medical preparation of the
13 endometrium prior to resection: Decapeptyl SR (triptorelin) versus
14 danazol versus placebo. *Minimally Invasive Therapy and Allied*
15 *Technologies: Mitat* 1998; 7:(3)251-6.
- 16 403. Erian MM, Thomas IL, Buck RJ *et al.* The effects of danazol after
17 endometrial resection. Results of a randomized, placebo-controlled,
18 double-blind study. *Australian and New Zealand Journal of Obstetrics*
19 *and Gynaecology* 1998; 38:(2)210-4.
- 20 404. Kriplani A, Manchanda R, Nath J *et al.* A randomized trial of danazol
21 pretreatment prior to endometrial resection. *European Journal of*
22 *Obstetrics, Gynecology, and Reproductive Biology* 2002; 103:(1)68-
23 71.
- 24 405. Jack SA, Cooper KG, Seymour J *et al.* A randomised controlled trial
25 of microwave endometrial ablation without endometrial preparation in
26 the outpatient setting: patient acceptability, treatment outcome and
27 costs. *BJOG: an International Journal of Obstetrics and Gynaecology*
28 2005; 112:(8)1109-16.
- 29 406. Alborzi S, Parsanezhad ME, and Dehbashi S. A comparison of
30 hysteroscopic endometrial ablation for abnormal uterine bleeding in
31 two groups of patients with or without endometrial preparation. *Middle*
32 *East Fertility Society Journal* 2002; 7:(2)-139.
- 33 407. Lissak A, Fruchter O, Mashlach S *et al.* Immediate versus delayed
34 treatment of perimenopausal bleeding due to benign causes by
35 balloon thermal ablation. *Journal of the American Association of*
36 *Gynecologic Laparoscopists* 1999; 6:(2)145-50.
- 37 408. Kriplani A, Manchanda R, Monga D *et al.* Depot medroxy
38 progesterone acetate: A poor preparatory agent for endometrial
39 resection. *Gynecologic and Obstetric Investigation* 2001; 52:(3)180-3.
- 40 409. Sculpher M, Thompson E, Brown J *et al.* A cost effectiveness
41 analysis of goserelin compared with danazol as endometrial thinning

- agents. *British Journal of Obstetrics and Gynaecology* 2000; 107:(3)340-6.
410. Crosignani PG, Vercellini P, Apolone G *et al.* Endometrial resection versus vaginal hysterectomy for menorrhagia: long-term clinical and quality-of-life outcomes. *American Journal of Obstetrics and Gynecology* 1997; 177:(1)95-101.
411. Dwyer N, Hutton J, and Stirrat GM. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for the surgical treatment of menorrhagia. *British Journal of Obstetrics and Gynaecology* 1993; 100:(3)-243.
412. Gannon MJ, Holt EM, Fairbank J *et al.* A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. *British Medical Journal* 1991; 303:(6814)1362-4.
413. Pinion SB, Parkin DE, Abramovich DR *et al.* Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. *British Medical Journal* 1994; 309:(6960)979-83.
414. Bain C, Cooper KG, and Parkin DE. Microwave endometrial ablation versus endometrial resection: a randomized controlled trial. *Obstetrics and Gynecology* 2002; 99:(6)983-7.
415. Hawe JA, Phillips AG, Chien PF *et al.* Cavaterm thermal balloon ablation for the treatment of menorrhagia.[erratum appears in BJOG 2000 Feb;107(2):295]. *British Journal of Obstetrics and Gynaecology* 1999; 106:(11)1143-8.
416. Gupta JK, Hickey M, Lumsden MA, Broder M, and Tsatsi LDR. Uterine artery embolisation for symptomatic uterine fibroids. (Cochrane Review). In: Cochrane Database of Systematic Reviews, Issue 4, 2005. Oxford: Update Software.
417. Edwards RG, Moss JG, Murray L, Lumsden MA, Twaddle S, and Murray GD. Randomised Study of Embolisation and Surgical Treatment for Uterine Fibroids (REST). No. CZH/4/1. Edinburgh: Chief Scientist Office; 2006.
418. Hehenkamp WJ, Volkers NA, Donderwinkel PF *et al.* Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2005; 193:(5)1618-29.
419. Hehenkamp WJ. Pain and Return to Daily Activities after Uterine Artery Embolization and Hysterectomy in the Treatment of Symptomatic Uterine Fibroids: Results from the Randomized EMMY

- 1 Trial. *Cardiovascular and Interventional Radiology* 2006; 29:(2)179-
2 87.
- 3 420. Pinto I, Chimeno P, Romo A *et al.* Uterine fibroids: uterine artery
4 embolization versus abdominal hysterectomy for treatment--a
5 prospective, randomized, and controlled clinical trial. *Radiology* 2003;
6 226:(2)425-31.
- 7 421. Spies JB, Allison S, Flick P *et al.* Spherical polyvinyl alcohol versus
8 tris-acryl gelatin microspheres for uterine artery embolization for
9 leiomyomas: results of a limited randomized comparative study.[see
10 comment]. *Journal of Vascular and Interventional Radiology* 2005;
11 16:(11)1431-7.
- 12 422. Spies JB, Allison S, Flick P *et al.* Polyvinyl alcohol particles and tris-
13 acryl gelatin microspheres for uterine artery embolization for
14 leiomyomas: Results of a randomized comparative study. *Journal of*
15 *Vascular and Interventional Radiology* 2004; 15:(8)793-800.
- 16 423. Vilos GA, Vilos AG, bu-Rafea B *et al.* Administration of goserelin
17 acetate after uterine artery embolization does not change the
18 reduction rate and volume of uterine myomas. *Fertility and Sterility*
19 2006; 85:(5)1478-83.
- 20 424. Worthington-Kirsch R, Spies JB, Myers ER *et al.* The Fibroid Registry
21 for outcomes data (FIBROID) for uterine embolization: short-term
22 outcomes.[erratum appears in *Obstet Gynecol.* 2005 Oct;106(4):869].
23 *Obstetrics and Gynecology* 2005; 106:(1)52-9.
- 24 425. Spies JB, Myers ER, Worthington-Kirsch R *et al.* The FIBROID
25 registry: Symptom and quality-of-life status 1 year after therapy.
26 *Obstetrics and Gynecology* 2005; 106:(6)1309-18.
- 27 426. Goodwin SC, Bradley LD, Lipman JC *et al.* Uterine artery
28 embolization versus myomectomy: A multicenter comparative study.
29 *Fertility and Sterility* 2006; 85:(1)14-21.
- 30 427. Katsumori T, Nakajima K, and Mihara T. Is a Large Fibroid a High-
31 Risk Factor for Uterine Artery Embolization? *American Journal of*
32 *Roentgenology* 2003; 181:(5)1309-14.
- 33 428. Prollius A, De VC, Loggenberg E *et al.* Uterine artery embolisation for
34 symptomatic fibroids: The effect of the large uterus on outcome.
35 *BJOG: an International Journal of Obstetrics and Gynaecology* 2004;
36 111:(3)239-42.
- 37 429. Society of Obstetricians and Gynaecologists of Canada. SOGC
38 clinical practice guidelines. Uterine fibroid embolization (UFE).
39 Number 150, October 2004. *International Journal of Gynaecology*
40 *and Obstetrics* 2005; 89:(3)305-18.

- 1 430. Spies JB, Cooper JM, Worthington-Kirsch R *et al.* Outcome of uterine
2 embolization and hysterectomy for leiomyomas: Results of a
3 multicenter study. *American Journal of Obstetrics and Gynecology*
4 2004; 191:(1)22-31.
- 5 431. Bruno J, Sterbis K, Flick P *et al.* Recovery after uterine artery
6 embolization for leiomyomas: A detailed analysis of its duration and
7 severity. *Journal of Vascular and Interventional Radiology* 2004;
8 15:(8)801-7.
- 9 432. Huang JYJ, Kafy S, Dugas A *et al.* Failure of uterine fibroid
10 embolization. *Fertility and Sterility* 2006; 85:(1)30-5.
- 11 433. Hutchins FL, Jr., Worthington-Kirsch R, and Berkowitz RP. Selective
12 uterine artery embolization as primary treatment for symptomatic
13 leiomyomata uteri. *Journal of the American Association of*
14 *Gynecologic Laparoscopists* 1999; 6:(3)279-84.
- 15 434. Katsumori T, Kasahara T, and Akazawa K. Long-term outcomes of
16 uterine artery embolization using gelatin sponge particles alone for
17 symptomatic fibroids.[see comment]. *AJR* 2006; American Journal of
18 Roentgenology. 186:(3)848-54.
- 19 435. Marret H, Cottier JP, Alonso AM *et al.* Predictive factors for fibroids
20 recurrence after uterine artery embolisation. *BJOG: an International*
21 *Journal of Obstetrics and Gynaecology* 2005; 112:(4)461-5.
- 22 436. McLucas B and Adler L. Uterine artery embolization as therapy for
23 myomata. *Infertility and Reproductive Medicine Clinics of North*
24 *America* 2000; 11:(1)77-94.
- 25 437. McLucas B, Adler L, and Perrella R. Predictive factors for success in
26 uterine fibroid embolisation. *Minimally Invasive Therapy and Allied*
27 *Technologies: Mitat* 1999; 8:(6)429-32.
- 28 438. McLucas B, Adler L, and Perrella R. Uterine fibroid embolization:
29 Nonsurgical treatment for symptomatic fibroids. *Journal of the*
30 *American College of Surgeons* 2001; 192:(1)95-105.
- 31 439. Pelage JP, Le DO, Soyer P *et al.* Fibroid-related menorrhagia:
32 treatment with superselective embolization of the uterine arteries and
33 midterm follow-up. *Radiology* 2000; 215:(2)428-31.
- 34 440. Pron G, Bennett J, Common A *et al.* The Ontario Uterine Fibroid
35 Embolization Trial. Part 2. Uterine fibroid reduction and symptom
36 relief after uterine artery embolization for fibroids. *Fertility and Sterility*
37 2003; 79:(1)120-7.
- 38 441. Pron G, Cohen M, Soucie J *et al.* The Ontario Uterine Fibroid
39 Embolization Trial. Part 1. Baseline patient characteristics, fibroid
40 burden, and impact on life. *Fertility and Sterility* 2003; 79:(1)112-9.

- 1 442. Pron G, Mocarski E, Bennett J *et al.* Tolerance, hospital stay, and
2 recovery after uterine artery embolization for fibroids: The Ontario
3 Uterine Fibroid Embolization Trial. *Journal of Vascular and*
4 *Interventional Radiology* 2003; 14:(10)1243-50.
- 5 443. Rajan DK, Beecroft JR, Clark TWI *et al.* Risk of intrauterine infectious
6 complications after uterine artery embolization. *Journal of Vascular*
7 *and Interventional Radiology* 2004; 15:(12)1415-21.
- 8 444. Ravina JH, Ciraru-Vigneron N, Aymard A *et al.* Uterine artery
9 embolisation for fibroid disease: Results of a 6 year study. *Minimally*
10 *Invasive Therapy and Allied Technologies: Mitat* 1999; 8:(6)441-7.
- 11 445. Roth AR, Spies JB, Walsh SM *et al.* Pain after uterine artery
12 embolization for leiomyomata: Can its severity be predicted and does
13 severity predict outcome? *Journal of Vascular and Interventional*
14 *Radiology* 2000; 11:(8)1047-52.
- 15 446. Shan H, Huang M-S, Guan S-H *et al.* Superselective uterine arterial
16 embolization with pingyangmycin-lipiodol emulsion for management
17 of symptomatic uterine leiomyoma. *Chinese Medical Journal* 2004;
18 117:(1)75-8.
- 19 447. Spies JB, Ascher SA, Roth AR *et al.* Uterine artery embolization for
20 leiomyomata. *Obstetrics and Gynecology* 2001; 98:(1)29-34.
- 21 448. Spies JB, Bruno J, Czeyda-Pommersheim F *et al.* Long-term
22 outcome of uterine artery embolization of leiomyomata. *Obstetrics*
23 *and Gynecology* 2005; 106:(5)933-9.
- 24 449. Spies JB, Roth AR, Jha RC *et al.* Leiomyomata treated with uterine
25 artery embolization: Factors associated with successful symptom and
26 imaging outcome. *Radiology* 2002; 222:(1)45-52.
- 27 450. Spies JB, Spector A, Roth AR *et al.* Complications after uterine artery
28 embolization for leiomyomas. *Obstetrics and Gynecology* 2002;
29 100:(5)873-80.
- 30 451. Walker W, Green A, and Sutton C. Bilateral uterine artery
31 embolisation for myomata: Results, complications and failures.
32 *Minimally Invasive Therapy and Allied Technologies: Mitat* 1999;
33 8:(6)449-54.
- 34 452. Walker WJ and Pelage JP. Uterine artery embolisation for
35 symptomatic fibroids: clinical results in 400 women with imaging
36 follow up. *BJOG: an International Journal of Obstetrics and*
37 *Gynaecology* 2002; 109:(11)1262-72.
- 38 453. Watson GM and Walker WJ. Uterine artery embolisation for the
39 treatment of symptomatic fibroids in 114 women: reduction in size of
40 the fibroids and women's views of the success of the treatment.

- 1 *BJOG: an International Journal of Obstetrics and Gynaecology* 2002;
2 109:(2)129-35.
- 3 454. Sawin SW, Pilevsky ND, Berlin JA *et al.* Comparability of
4 perioperative morbidity between abdominal myomectomy and
5 hysterectomy for women with uterine leiomyomas. *American Journal*
6 *of Obstetrics and Gynecology* 2000; 183:(6)1448-55.
- 7 455. Broder MS, Goodwin S, Chen G *et al.* Comparison of long-term
8 outcomes of myomectomy and uterine artery embolization. *Obstetrics*
9 *and Gynecology* 2002; 100:(5)864-8.
- 10 456. Loffer FD. Improving results of hysteroscopic submucosal
11 myomectomy for menorrhagia by concomitant endometrial ablation.
12 *Journal of Minimally Invasive Gynecology* 2005; 12:(3)254-60.
- 13 457. Derman SG, Rehnstrom J, and Neuwirth RS. The long-term
14 effectiveness of hysteroscopic treatment of menorrhagia and
15 leiomyomas. *Obstetrics and Gynecology* 1991; 77:(4)591-4.
- 16 458. Liu WM, Tzeng CR, Yi-Jen C *et al.* Combining the uterine depletion
17 procedure and myomectomy may be useful for treating symptomatic
18 fibroids. *Fertility and Sterility* 2004; 82:(1)205-10.
- 19 459. Seracchioli R, Rossi S, Govoni F *et al.* Fertility and obstetric outcome
20 after laparoscopic myomectomy of large myomata: a randomized
21 comparison with abdominal myomectomy. *Human Reproduction*
22 2000; 15:(12)2663-8.
- 23 460. Stringer NH, Walker JC, and Meyer PM. Comparison of 49
24 laparoscopic myomectomies with 49 open myomectomies. *Journal of*
25 *the American Association of Gynecologic Laparoscopists* 1997;
26 4:(4)457-64.
- 27 461. Cravello L, Farnarier J, de MR *et al.* Hysteroscopic resection of
28 fibroids: Results with a 6-year follow-up period. *Journal of*
29 *Gynecologic Surgery* 1999; 15:(1)1-5.
- 30 462. Vercellini P, Zaina B, Yaylayan L *et al.* Hysteroscopic myomectomy:
31 Long-term effects on menstrual pattern and fertility. *Obstetrics and*
32 *Gynecology* 1999; 94:(3)341-7.
- 33 463. De BS, Dijkman AB, and Hemrika DJ. Transcervical resection of
34 fibroids (TCRM): Results related to hysteroscopic classification.
35 *Gynaecological Endoscopy* 1995; 4:(4)-246.
- 36 464. Marziani R, Mossa B, Ebano V *et al.* Transcervical hysteroscopic
37 myomectomy: Long-term effects on abnormal uterine bleeding.
38 *Clinical and Experimental Obstetrics and Gynecology* 2005; 32:(1)23-
39 6.

- 1 465. Olufowobi O, Sharif K, Papaionnou S *et al.* Are the anticipated
2 benefits of myomectomy achieved in women of reproductive age? A
3 5-year review of the results at a UK tertiary hospital. *Journal of*
4 *Obstetrics and Gynaecology* 2004; 24:(4)434-40.
- 5 466. Reilly RJ and Nour N. Abdominal myomectomy is associated with few
6 surgical complications. *Journal of Gynecologic Techniques* 1998;
7 4:(3)-112.
- 8 467. Lethaby A, Vollenhoven B, and Sowter M. Pre-operative GnRH
9 analogue therapy before hysterectomy or myomectomy for uterine
10 fibroids. (Cochrane Review). In: Cochrane Database of Systematic
11 Reviews, Issue 2, 2001. Oxford: Update Software.
- 12 468. Agostini A, Ronda I, Franchi F *et al.* Oxytocin during myomectomy: A
13 randomized study. *European Journal of Obstetrics, Gynecology, and*
14 *Reproductive Biology* 2005; 118:(2)235-8.
- 15 469. Celik H and Sapmaz E. Use of a single preoperative dose of
16 misoprostol is efficacious for patients who undergo abdominal
17 myomectomy. *Fertility and Sterility* 2003; 79:(5)1207-10.
- 18 470. Corson SL, Brooks PG, Serden SP *et al.* Effects of vasopressin
19 administration during hysteroscopic surgery. *Journal of Reproductive*
20 *Medicine* 1994; 39:(6)419-23.
- 21 471. Fedele L, Vercellini P, Bianchi S *et al.* Treatment with GnRH agonists
22 before myomectomy and the risk of short-term myoma recurrence.
23 *British Journal of Obstetrics and Gynaecology* 1990; 97:(5)393-6.
- 24 472. Fletcher H, Frederick J, Hardie M *et al.* A randomized comparison of
25 vasopressin and tourniquet as hemostatic agents during
26 myomectomy. *Obstetrics and Gynecology* 1996; 87:(6)1014-8.
- 27 473. Frederick J, Fletcher H, Simeon D *et al.* Intramyometrial vasopressin
28 as a haemostatic agent during myomectomy. *British Journal of*
29 *Obstetrics and Gynaecology* 1994; 101:(5)435-7.
- 30 474. Ginsburg ES, Benson CB, Garfield JM *et al.* The effect of operative
31 technique and uterine size on blood loss during myomectomy: A
32 prospective randomized study. *Fertility and Sterility* 1993; 60:(6)956-
33 62.
- 34 475. Jasonni VM, D'Anna R, Mancuso A *et al.* Randomized double-blind
35 study evaluating the efficacy on uterine fibroids shrinkage and on
36 intra-operative blood loss of different length of leuprolide acetate
37 depot treatment before myomectomy. *Acta Obstetrica et*
38 *Gynecologica Scandinavica* 2001; 80:(10)956-8.
- 39 476. Palomba S, Morelli M, Noia R *et al.* Short-term administration of
40 tibolone plus GnRH analog before laparoscopic myomectomy.

- 1 *Journal of the American Association of Gynecologic Laparoscopists*
2 2002; 9:(2)170-4.
- 3 477. Vercellini P, Trespidi L, Zaina B *et al.* Gonadotropin-releasing
4 hormone agonist treatment before abdominal myomectomy: a
5 controlled trial. *Fertility and Sterility* 2003; 79:(6)1390-5.
- 6 478. Zullo F, Palomba S, Corea D *et al.* Bupivacaine plus epinephrine for
7 laparoscopic myomectomy: A randomized placebo-controlled trial.
8 *Obstetrics and Gynecology* 2004; 104:(2)243-9.
- 9 479. Lefebvre G, Allaire C, Jeffrey J *et al.* SOGC clinical guidelines.
10 Hysterectomy [French]. *Journal of Obstetrics and Gynaecology*
11 *Canada: JOGC* 2002; 24:(1)37-61.
- 12 480. Schilling J, Wyss P, Faisst K *et al.* Swiss consensus guidelines for
13 hysterectomy. Swiss Society of Gynecology and Obstetrics,
14 Switzerland. *International Journal of Gynaecology and Obstetrics*
15 1999; 64:(3)297-305.
- 16 481. Hurskainen R, Teperi J, Aalto AM *et al.* Levonorgestrel-releasing
17 intrauterine system or hysterectomy in the treatment of essential
18 menorrhagia: Predictors of outcome. *Acta Obstetrica et*
19 *Gynecologica Scandinavica* 2004; 83:(4)401-3.
- 20 482. Nagele F, Rubinger T, and Magos A. Why do women choose
21 endometrial ablation rather than hysterectomy? *Fertility and Sterility*
22 1998; 69:(6)1063-6.
- 23 483. Mingo C, Herman CJ, and Jasperse M. Women's stories: Ethnic
24 variations in women's attitudes and experiences of menopause,
25 hysterectomy, and hormone replacement therapy. *Journal of*
26 *Womens Health and Gender-Based Medicine* 2000; 9:(SUPPL.
27 2)S27-S38.
- 28 484. Nathorst-Boos J, Fuchs T, and von Schoultz B. Consumer's attitude
29 to hysterectomy: The experience of 678 women. *Acta Obstetrica et*
30 *Gynecologica Scandinavica* 1992; 71:(3)230-4.
- 31 485. Johnson N, Barlow D, Lethaby A, Tavender E, Curr E, and Garry R.
32 Surgical approach to hysterectomy for benign gynaecological
33 disease. (Cochrane Review). In: Cochrane Database of Systematic
34 Reviews, Issue 2, 2006. Oxford: Update Software.
- 35 486. Cheng YL, Jia HF, Wei CC *et al.* Comparison of total laparoscopic
36 hysterectomy and laparoscopically assisted vaginal hysterectomy.
37 *Gynecologic and Obstetric Investigation* 2002; 53:(4)214-9.
- 38 487. Darai E, Soriano D, Kimata P *et al.* Vaginal hysterectomy for enlarged
39 uteri, with or without laparoscopic assistance: randomized study.
40 *Obstetrics and Gynecology* 2001; 97:(5 Pt 1)712-6.

- 1 488. Ellstrom M, Ferraz-Nunes J, Hahlin M *et al.* A randomized trial with a
2 cost-consequence analysis after laparoscopic and abdominal
3 hysterectomy. *Obstetrics and Gynecology* 1998; 91:(1)30-4.
- 4 489. Ellstrom M, Olsen MF, Olsson JH *et al.* Pain and pulmonary function
5 following laparoscopic and abdominal hysterectomy: a randomized
6 study. *Acta Obstetrica et Gynecologica Scandinavica* 1998;
7 77:(9)923-8.
- 8 490. Ellstrom MA, Astrom M, Moller A *et al.* A randomized trial comparing
9 changes in psychological well-being and sexuality after laparoscopic
10 and abdominal hysterectomy. *Acta Obstetrica et Gynecologica*
11 *Scandinavica* 2003; 82:(9)871-5.
- 12 491. Falcone T, Paraiso MF, and Mascha E. Prospective randomized
13 clinical trial of laparoscopically assisted vaginal hysterectomy versus
14 total abdominal hysterectomy. *American Journal of Obstetrics and*
15 *Gynecology* 1999; 180:(4)955-62.
- 16 492. Ferrari MM, Berlanda N, Mezzopane R *et al.* Identifying the
17 indications for laparoscopically assisted vaginal hysterectomy: a
18 prospective, randomised comparison with abdominal hysterectomy in
19 patients with symptomatic uterine fibroids. *BJOG: an International*
20 *Journal of Obstetrics and Gynaecology* 2000; 107:(5)620-5.
- 21 493. Garry R, Fountain J, Mason S *et al.* The eVALuate study: two parallel
22 randomised trials, one comparing laparoscopic with abdominal
23 hysterectomy, the other comparing laparoscopic with vaginal
24 hysterectomy.[erratum appears in BMJ. 2004 Feb 28;328(7438):494].
25 *British Medical Journal* 2004; 328:(7432)129-33.
- 26 494. Harkki-Siren P, Sjoberg J, Toivonen J *et al.* Clinical outcome and
27 tissue trauma after laparoscopic and abdominal hysterectomy: a
28 randomized controlled study. *Acta Obstetrica et Gynecologica*
29 *Scandinavica* 2000; 79:(10)866-71.
- 30 495. Hwang JL, Seow KM, Tsai YL *et al.* Comparative study of vaginal,
31 laparoscopically assisted vaginal and abdominal hysterectomies for
32 uterine myoma larger than 6 cm in diameter or uterus weighing at
33 least 450 g: A prospective randomized study. *Acta Obstetrica et*
34 *Gynecologica Scandinavica* 2002; 81:(12)1132-8.
- 35 496. Langebrekke A, Eraker R, Nesheim BI *et al.* Abdominal hysterectomy
36 should not be considered as a primary method for uterine removal. A
37 prospective randomised study of 100 patients referred to
38 hysterectomy. *Acta Obstetrica et Gynecologica Scandinavica* 1996;
39 75:(4)404-7.
- 40 497. Learman LA, Summitt RL, Jr., Varner RE *et al.* A randomized
41 comparison of total or supracervical hysterectomy: surgical

- 1 complications and clinical outcomes. *Obstetrics and Gynecology*
2 2003; 102:(3)453-62.
- 3 498. Lumsden MA, Twaddle S, Hawthorn R *et al.* A randomised
4 comparison and economic evaluation of laparoscopic-assisted
5 hysterectomy and abdominal hysterectomy. *BJOG: an International*
6 *Journal of Obstetrics and Gynaecology* 2000; 107:(11)1386-91.
- 7 499. Marana R, Busacca M, Zupi E *et al.* Laparoscopically assisted
8 vaginal hysterectomy versus total abdominal hysterectomy: a
9 prospective, randomized, multicenter study. *American Journal of*
10 *Obstetrics and Gynecology* 1999; 180:(2 Pt 1)270-5.
- 11 500. Miskry T and Magos A. Randomized, prospective, double-blind
12 comparison of abdominal and vaginal hysterectomy in women without
13 uterovaginal prolapse. *Acta Obstetrica et Gynecologica Scandinavica*
14 2003; 82:(4)351-8.
- 15 501. Olsson JH, Ellstrom M, and Hahlin M. A randomised prospective trial
16 comparing laparoscopic and abdominal hysterectomy. *British Journal*
17 *of Obstetrics and Gynaecology* 1996; 103:(4)345-50.
- 18 502. Ottosen C, Lingman G, and Ottosen L. Three methods for
19 hysterectomy: a randomised, prospective study of short term
20 outcome. *BJOG: an International Journal of Obstetrics and*
21 *Gynaecology* 2000; 107:(11)1380-5.
- 22 503. Perino A, Cucinella G, Venezia R *et al.* Total laparoscopic
23 hysterectomy versus total abdominal hysterectomy: an assessment of
24 the learning curve in a prospective randomized study. *Human*
25 *Reproduction* 1999; 14:(12)2996-9.
- 26 504. Raju KS and Auld BJ. A randomised prospective study of
27 laparoscopic vaginal hysterectomy versus abdominal hysterectomy
28 each with bilateral salpingo-oophorectomy. *British Journal of*
29 *Obstetrics and Gynaecology* 1994; 101:(12)1068-71.
- 30 505. Ribeiro SC, Ribeiro RM, Santos NC *et al.* A randomized study of total
31 abdominal, vaginal and laparoscopic hysterectomy. *International*
32 *Journal of Gynaecology and Obstetrics* 2003; 83:(1)37-43.
- 33 506. Richardson RE, Bournas N, and Magos AL. Is laparoscopic
34 hysterectomy a waste of time? *Lancet* 1995; 345:(8941)36-41.
- 35 507. Schutz K, Possover M, Merker A *et al.* Prospective randomized
36 comparison of laparoscopic-assisted vaginal hysterectomy (LAVH)
37 with abdominal hysterectomy (AH) for the treatment of the uterus
38 weighing >200 g. *Surgical Endoscopy* 2002; 16:(1)121-5.
- 39 508. Seracchioli R, Venturoli S, Vianello F *et al.* Total laparoscopic
40 hysterectomy compared with abdominal hysterectomy in the

- 1 presence of a large uterus. *Journal of the American Association of*
 2 *Gynecologic Laparoscopists* 2002; 9:(3)333-8.
- 3 509. Soriano D, Goldstein A, Lecuru F *et al.* Recovery from vaginal
 4 hysterectomy compared with laparoscopy-assisted vaginal
 5 hysterectomy: a prospective, randomized, multicenter study. *Acta*
 6 *Obstetrica et Gynecologica Scandinavica* 2001; 80:(4)337-41.
- 7 510. Summitt RL, Jr., Stovall TG, Lipscomb GH *et al.* Randomized
 8 comparison of laparoscopy-assisted vaginal hysterectomy with
 9 standard vaginal hysterectomy in an outpatient setting. *Obstetrics*
 10 *and Gynecology* 1992; 80:(6)895-901.
- 11 511. Summitt RL, Jr., Stovall TG, Steege JF *et al.* A multicenter
 12 randomized comparison of laparoscopically assisted vaginal
 13 hysterectomy and abdominal hysterectomy in abdominal
 14 hysterectomy candidates. *Obstetrics and Gynecology* 1998;
 15 92:(3)321-6.
- 16 512. Choy CM, Lau WC, Tam WH *et al.* A randomised controlled trial of
 17 intramuscular syntometrine and intravenous oxytocin in the
 18 management of the third stage of labour. *BJOG: an International*
 19 *Journal of Obstetrics and Gynaecology* 2002; 109:(2)173-7.
- 20 513. Yuen PM, Mak TW, Yim SF *et al.* Metabolic and inflammatory
 21 responses after laparoscopic and abdominal hysterectomy. *American*
 22 *Journal of Obstetrics and Gynecology* 1998; 179:(1)1-5.
- 23 514. Aka N, Kose G, Gonenc I *et al.* Tissue trauma after vaginal
 24 hysterectomy and colporrhaphy versus abdominal hysterectomy: A
 25 randomised controlled study. *Australian and New Zealand Journal of*
 26 *Obstetrics and Gynaecology* 2004; 44:(4)328-31.
- 27 515. Benassi L, Rossi T, Kaihura CT *et al.* Abdominal or vaginal
 28 hysterectomy for enlarged uteri: a randomized clinical trial. *American*
 29 *Journal of Obstetrics and Gynecology* 2002; 187:(6)1561-5.
- 30 516. Gimbel H, Zobbe V, Andersen BM *et al.* Randomised controlled trial
 31 of total compared with subtotal hysterectomy with one-year follow up
 32 results. *BJOG: an International Journal of Obstetrics and*
 33 *Gynaecology* 2003; 110:(12)1088-98.
- 34 517. Gimbel H, Zobbe V, Andersen BJ *et al.* Lower urinary tract symptoms
 35 after total and subtotal hysterectomy: results of a randomized
 36 controlled trial. *International Urogynecology Journal* 2005; 16:(4)257-
 37 62.
- 38 518. Thakar R, Ayers S, Clarkson P *et al.* Outcomes after total versus
 39 subtotal abdominal hysterectomy. *New England Journal of Medicine*
 40 2002; 347:(17)1318-25.

- 1 519. Kuppermann M, Summitt RL, Jr., Varner RE *et al.* Sexual functioning
2 after total compared with supracervical hysterectomy: a randomized
3 trial. *Obstetrics and Gynecology* 2005; 105:(6)1309-18.
- 4 520. McPherson K, Metcalfe MA, Herbert A *et al.* Severe complications of
5 hysterectomy: The VALUE study. *BJOG: an International Journal of*
6 *Obstetrics and Gynaecology* 2004; 111:(7)688-94.
- 7 521. Maresh MJ, Metcalfe MA, McPherson K *et al.* The VALUE national
8 hysterectomy study: description of the patients and their surgery.
9 *BJOG: an International Journal of Obstetrics and Gynaecology* 2002;
10 109:(3)302-12.
- 11 522. Varol N, Healey M, Tang P *et al.* Ten-year review of hysterectomy
12 morbidity and mortality: can we change direction? *Australian and*
13 *New Zealand Journal of Obstetrics and Gynaecology* 2001;
14 41:(3)295-302.
- 15 523. Meikle SF, Nugent EW, and Orleans M. Complications and recovery
16 from laparoscopy-assisted vaginal hysterectomy compared with
17 abdominal and vaginal hysterectomy. *Obstetrics and Gynecology*
18 1997; 89:(2)304-11.
- 19 524. Kjerulff KH, Langenberg PW, Rhodes JC *et al.* Effectiveness of
20 hysterectomy. *Obstetrics and Gynecology* 2000; 95:(3)319-26.
- 21 525. Garry R, Fountain J, Brown J *et al.* EVALUATE hysterectomy trial: a
22 multicentre randomised trial comparing abdominal, vaginal and
23 laparoscopic methods of hysterectomy. *Health Technology*
24 *Assessment* 2004; 8:(26)1-154.
- 25 526. Ylikorkala O, Tiitinen A, Hulkko S *et al.* Decrease in symptoms, blood
26 loss and uterine size with nafarelin acetate before abdominal
27 hysterectomy: a placebo-controlled, double-blind study. *Human*
28 *Reproduction* 1995; 10:(6)1470-4.
- 29 527. Weeks AD, Duffy SR, and Walker JJ. A double-blind randomised trial
30 of leuprorelin acetate prior to hysterectomy for dysfunctional uterine
31 bleeding. *BJOG: an International Journal of Obstetrics and*
32 *Gynaecology* 2000; 107:(3)323-8.
- 33 528. Yuen PM and Rogers MS. Is laparoscopically-assisted vaginal
34 hysterectomy associated with low operative morbidity? *Australian and*
35 *New Zealand Journal of Obstetrics and Gynaecology* 1996; 36:(1)39-
36 43.
- 37 529. Scottish Intercollegiate Guidelines Network. Epithelial ovarian cancer.
38 2003. Edinburgh, Scottish Intercollegiate Guidelines Network.
- 39 530. Whittemore AS, Harris R, and Itnyre J. Characteristics relating to
40 ovarian cancer risk: collaborative analysis of 12 US case-control
41 studies. II. Invasive epithelial ovarian cancers in white women.

- 1 Collaborative Ovarian Cancer Group. *American Journal of*
2 *Epidemiology* 1992; 136:(10)1184-203.
- 3 531. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2
4 mutation carriers. The Breast Cancer Linkage Consortium. *Journal of*
5 *the National Cancer Institute* 1999; 91:(15)1310-6.
- 6 532. Aarnio M, Sankila R, Pukkala E *et al.* Cancer risk in mutation carriers
7 of DNA-mismatch-repair genes. *International Journal of Cancer* 1999;
8 81:(2)214-8.
- 9 533. Rebbeck TR, Lynch HT, Neuhausen SL *et al.* Prophylactic
10 oophorectomy in carriers of BRCA1 or BRCA2 mutations. *New*
11 *England Journal of Medicine* 2002; 346:(21)1616-22.
- 12 534. Averette HE and Nguyen HN. The role of prophylactic oophorectomy
13 in cancer prevention. *Gynecologic Oncology* 1994; 55:(3 Pt 2)S38-
14 S41.
- 15 535. NIH Consensus Development Panel on Ovarian Cancer. NIH
16 consensus conference. Ovarian cancer. Screening, treatment, and
17 follow-up. NIH Consensus Development Panel on Ovarian Cancer.
18 *JAMA: the journal of the American Medical Association* 1995;
19 273:(6)491-7.
- 20 536. Stratton JF, Pharoah P, Smith SK *et al.* A systematic review and
21 meta-analysis of family history and risk of ovarian cancer. *British*
22 *Journal of Obstetrics and Gynaecology* 1998; 105:(5)493-9.
- 23 537. Wagner TM, Moslinger R, Langbauer G *et al.* Attitude towards
24 prophylactic surgery and effects of genetic counselling in families with
25 BRCA mutations. Austrian Hereditary Breast and Ovarian Cancer
26 Group. *British Journal of Cancer* 2000; 82:(7)1249-53.
- 27 538. Hallowell N. A qualitative study of the information needs of high-risk
28 women undergoing prophylactic oophorectomy. *Psycho-Oncology*
29 2000; 9:(6)486-95.
- 30 539. Ballard LA and Walters MD. Transvaginal mobilization and removal of
31 ovaries and fallopian tubes after vaginal hysterectomy. *Obstetrics and*
32 *Gynecology* 1996; 87:(1)35-9.
- 33 540. Davies A, O'Connor H, and Magos AL. A prospective study to
34 evaluate oophorectomy at the time of vaginal hysterectomy. *British*
35 *Journal of Obstetrics and Gynaecology* 1996; 103:(9)915-20.
- 36 541. Bhavnani V and Clarke A. Women awaiting hysterectomy: a
37 qualitative study of issues involved in decisions about oophorectomy.
38 *BJOG: an International Journal of Obstetrics and Gynaecology* 2003;
39 110:(2)168-74.

- 1 542. Overton C, Hargreaves J, and Maresh M. A national survey of the
2 complications of endometrial destruction for menstrual disorders: the
3 M.I.S.T.L.E.T.O.E. study. Manchester: The Clinical Audit Unit, The
4 Royal College of Obstetricians and Gynaecologists, St Mary's
5 Hospital for Women and Children; 1997.
- 6 543. Abramovich DR, Kitchener HC, Parkin DE *et al.* A Scottish audit of
7 hysteroscopic surgery for menorrhagia: Complications and follow up.
8 *British Journal of Obstetrics and Gynaecology* 1995; Vol. 102:(3)249-
9 54.
- 10 544. Spies J, Niedzwiecki G, Goodwin S *et al.* Training standards for
11 physicians performing uterine artery embolization for leiomyomata:
12 consensus statement developed by the Task Force on Uterine Artery
13 Embolization and the standards division of the Society of
14 Cardiovascular & Interventional Radiology--August 2000. *Journal of*
15 *Vascular and Interventional Radiology* 2001; 12:(1)19-21.
- 16 545. Royal College of Radiologists. Sub-Speciality Training Curricula:
17 Interventional Radiology. Royal College of Radiologists [online] 2006
18 Available from: URL: <http://www.rcr.ac.uk/index.asp?PageID=530>
- 19 546. Spies JB and Sacks D. Credentials for uterine artery embolization.
20 *Journal of Vascular and Interventional Radiology* 2004; 15:(2 Pt
21 1)111-3.
- 22 547. Arndt M, Bradbury RC, and Golec JH. Surgeon volume and hospital
23 resource utilization. *Inquiry* 1995; 32:(4)407-17.
- 24 548. Altgassen C, Michels W, and Schneider A. Learning laparoscopic-
25 assisted hysterectomy. *Obstetrics and Gynecology* 2004; 104:(2)308-
26 13.
- 27 549. Luft HS, Hunt SS, and Maerki SC. The volume-outcome relationship:
28 practice-makes-perfect or selective-referral patterns? *Health Services*
29 *Research* 1987; 22:(2)157-82.
- 30 550. Roos LL, Jr., Cageorge SM, Roos NP *et al.* Centralization,
31 certification, and monitoring. Readmissions and complications after
32 surgery. *Medical Care* 1986; 24:(11)1044-66.
- 33 551. Sculpher M. A cost-utility analysis of abdominal hysterectomy versus
34 transcervical endometrial resection for the surgical treatment of
35 menorrhagia. *International Journal of Technology Assessment in*
36 *Health Care* 1998; 14:(2)302-19.
- 37 552. Cooper KG, Jack SA, Parkin DE *et al.* Five-year follow up of women
38 randomised to medical management or transcervical resection of the
39 endometrium for heavy menstrual loss: clinical and quality of life
40 outcomes. *BJOG: an International Journal of Obstetrics and*
41 *Gynaecology* 2001; 108:(12)1222-8.

- 1 553. Dijkhuizen FPHL, Mol BWJ, Bongers MY *et al.* Cost-effectiveness of
2 transvaginal sonography and saline infused sonography in the
3 evaluation of menorrhagia. *International Journal of Gynecology and*
4 *Obstetrics* 2003; 83:(1)45-52.
- 5 554. Nuffield Institute for Health and NHS Centre for Reviews and
6 Dissemination. Hospital volume and health care outcomes, costs and
7 patient access. *Effective Health Care* 1996; 2:(8)1-16.
- 8 555. Halm EA, Lee C, and Chassin MR. Is volume related to outcome in
9 health care? A systematic review and methodologic critique of the
10 literature. *Annals of Internal Medicine* 2002; 137:(6)511-20.
- 11 556. Khuri SF, Hussaini BE, Kumbhani DJ *et al.* Does volume help predict
12 outcome in surgical disease?. *Advances in Surgery* 2005; 39:379-
13 453.
- 14 557. Sculpher M, Manca A, Abbott J *et al.* Cost effectiveness analysis of
15 laparoscopic hysterectomy compared with standard hysterectomy:
16 Results from a randomised trial. *British Medical Journal* 2004;
17 328:(7432)134.
- 18 558. Cameron IM, Mollison J, Pinion B *et al.* A cost comparison of
19 hysterectomy and hysteroscopic surgery for the treatment of
20 menorrhagia. *European Journal of Obstetrics, Gynecology, and*
21 *Reproductive Biology* 1996; 70:(1)87-92.
- 22 559. Garside R, Stein K, Wyatt K *et al.* A cost-utility analysis of microwave
23 and thermal balloon endometrial ablation techniques for the treatment
24 of heavy menstrual bleeding. *BJOG: an International Journal of*
25 *Obstetrics and Gynaecology* 2004; 111:(10)1103-14.
- 26 560. Philipp CS, Dilley A, Miller CH *et al.* Platelet functional defects in
27 women with unexplained menorrhagia. *Journal of Thrombosis and*
28 *Haemostasis* 2003; 1:(3)477-84.
- 29 561. Vercellini P, De Giorgi O, Aimi G *et al.* Menstrual characteristics in
30 women with and without endometriosis. *Obstetrics and Gynecology*
31 1997; 90:(2)264-8.
- 32 562. Miller CH, Dilley A, Richardson L *et al.* Population differences in von
33 Willebrand factor levels affect the diagnosis of von Willebrand
34 disease in African-American women. *American Journal of*
35 *Hematology* 2001; 67:(2)125-9.
- 36 563. Friberg B, Orno AK, Lindgren A *et al.* Bleeding disorders among
37 young women: a population-based prevalence study. *Acta Obstetrica*
38 *et Gynecologica Scandinavica* 2006; 85:(2)200-6.
- 39 564. Philipp CS, Faiz A, Bowling N *et al.* Age and the prevalence of
40 bleeding disorders in women with menorrhagia. *Obstetrics and*
41 *Gynecology* 2005; 105:(1)61-6.

- 1 565. Dilley A, Drews C, Miller C *et al.* von Willebrand disease and other
2 inherited bleeding disorders in women with diagnosed menorrhagia.
3 *Obstetrics and Gynecology* 2001; 97:(4)630-6.
- 4 566. Fraser IS, Warner P, and Marantos PA. Estimating menstrual blood
5 loss in women with normal and excessive menstrual fluid volume.
6 *Obstetrics and Gynecology* 2001; 98:(5)806-14.
- 7 567. Redman CWE, McFarlane T, Cottrell D *et al.* Improving
8 communication between doctors and patients having a hysterectomy.
9 *Journal of Obstetrics and Gynaecology* 1986; 6:(4)275-6.
- 10 568. Bettocchi S, Ceci O, Vicino M *et al.* Diagnostic inadequacy of
11 dilatation and curettage. *Fertility and Sterility* 2001; 75:(4)803-5.
- 12 569. Fothergill DJ, Brown VA, and Hill AS. Histological sampling of the
13 endometrium--a comparison between formal curettage and the
14 Pipelle sampler. *British Journal of Obstetrics & Gynaecology* 1992;
15 99:(9)779-80.
- 16 570. Goldchmit R, Katz Z, Blickstein I *et al.* The accuracy of endometrial
17 Pipelle sampling with and without sonographic measurement of
18 endometrial thickness. *Obstetrics & Gynecology* 1993; 82:(5)727-30.
- 19 571. Hunter DC and McClure N. Abnormal uterine bleeding: an evaluation
20 endometrial biopsy, vaginal ultrasound and outpatient hysteroscopy.
21 *Ulster Medical Journal* 2001; 70:(1)25-30.
- 22 572. Philipp CS, Miller CH, Faiz A *et al.* Screening women with
23 menorrhagia for underlying bleeding disorders: the utility of the
24 platelet function analyser and bleeding time. *Haemophilia*. 2005;
25 11:(5)497-503.
- 26 573. West CP, Lumsden MA, Hillier H *et al.* Potential role for
27 medroxyprogesterone acetate as an adjunct to goserelin (Zoladex) in
28 the medical management of uterine fibroids. *Human Reproduction*
29 1992; 7:(3)328-32.
- 30 574. Vuorma S, Rissanen P, Aalto AM *et al.* Factors predicting choice of
31 treatment for menorrhagia in gynaecology outpatient clinics. *Social*
32 *Science and Medicine* 2003; 56:(8)1653-60.
- 33 575. Razavi MK, Hwang G, Jahed A *et al.* Abdominal myomectomy versus
34 uterine fibroid embolization in the treatment of symptomatic uterine
35 leiomyomas. *AJR* 2003; 180:(6)1571-5.
- 36 576. Phillips DR, Nathanson HG, Meltzer SM *et al.* Transcervical
37 electrosurgical resection of submucous leiomyomas for chronic
38 menorrhagia.[erratum appears in J Am Assoc Gynecol Laparosc
39 1995 Aug;2(4):496]. *Journal of the American Association of*
40 *Gynecologic Laparoscopists* 1995; 2:(2)147-53.

- 1 577. Sapmaz E and Celik H. Comparison of the effects of the ligation of
2 ascending branches of bilateral arteria uterina with tourniquet method
3 on the intra-operative and post-operative hemorrhage in abdominal
4 myomectomy cases. *European Journal of Obstetrics, Gynecology,*
5 *and Reproductive Biology* 2003; 111:(1)74-7.
- 6 578. Taylor A, Sharma M, Tsirkas P *et al.* Reducing blood loss at open
7 myomectomy using triple tourniquets: A randomised controlled trial.
8 *BJOG: an International Journal of Obstetrics and Gynaecology* 2005;
9 112:(3)340-5.
- 10 579. Anonymous. ACOG criteria set. Hysterectomy, abdominal or vaginal
11 for abnormal uterine bleeding. Number 28, November 1997.
12 Committee on Quality Assessment. American College of
13 Obstetricians and Gynecologists. *International Journal of*
14 *Gynaecology and Obstetrics* 1998; 60:(3)314-5.
- 15 580. Casey MJ, Garcia-Padial J, Johnson C *et al.* A critical analysis of
16 laparoscopic assisted vaginal hysterectomies compared with vaginal
17 hysterectomies unassisted by laparoscopy and transabdominal
18 hysterectomies. *Journal of Gynecologic Surgery* 1994; 10:(1)7-14.
- 19 581. Falkeborn M, Schairer C, Naessen T *et al.* Risk of myocardial
20 infarction after oophorectomy and hysterectomy. *Journal of Clinical*
21 *Epidemiology* 2000; 53:(8)832-7.
- 22 582. Harmanli OH, Gentzler CK, Byun S *et al.* A comparison of abdominal
23 and vaginal hysterectomy for the large uterus. *International Journal of*
24 *Gynaecology and Obstetrics* 2004; 87:(1)19-23.
- 25 583. Iversen L, Hannaford PC, Elliott AM *et al.* Long term effects of
26 hysterectomy on mortality: Nested cohort study. *British Medical*
27 *Journal* 2005; 330:(7506)1482-5.
- 28 584. Kung FT, Hwang FR, Lin H *et al.* Comparison of laparoscopically
29 assisted vaginal hysterectomy and abdominal hysterectomy in
30 taiwan. *Journal of the Formosan Medical Association* 1996;
31 95:(10)769-75.
- 32 585. Martel MJ and Gilliland GB. Laparoscopically assisted vaginal
33 hysterectomy: A review of 106 cases. *Journal of Laparoendoscopic*
34 *Surgery* 1995; 5:(6)371-5.
- 35 586. Mehra S, Bhat V, and Mehra G. Laparoscopic vs. Abdominal vs.
36 Vaginal hysterectomy. *Gynaecological Endoscopy* 1999; 8:(1)29-34.
- 37 587. Neumann G, Olesen PG, Hansen V *et al.* The short-term prevalence
38 of de novo urinary symptoms after different modes of hysterectomy.
39 *International Urogynecology Journal* 2004; 15:(1)14-9.
- 40 588. Seracchioli R, Venturoli S, Colombo FM *et al.* GnRH agonist
41 treatment before total laparoscopic hysterectomy for large uteri.

- 1 *Journal of the American Association of Gynecologic Laparoscopists*
2 2003; 10:(3)316-9.
- 3 589. Unger JB, Paul R, and Caldito G. Hysterectomy for the massive
4 leiomyomatous uterus. *Obstetrics and Gynecology* 2002;
5 100:(6)1271-5.
- 6 590. Wattiez A, Soriano D, Fiaccavento A *et al.* Total laparoscopic
7 hysterectomy for very enlarged uteri. *Journal of the American*
8 *Association of Gynecologic Laparoscopists* 2002; 9:(2)125-30.
- 9 591. De Meeus JB and Magnin G. Indications of laparoscopic
10 hysterectomy. *European Journal of Obstetrics, Gynecology, and*
11 *Reproductive Biology* 1997; 74:(1)49-52.
- 12 592. Erian J, El-Toukhy T, Chandakas S *et al.* One hundred cases of
13 laparoscopic subtotal hysterectomy using the PK and Lap Loop
14 systems. *Journal of Minimally Invasive Gynecology* 2005; 12:(4)365-
15 9.
- 16 593. Gath D, Rose N, Bond A *et al.* Hysterectomy and psychiatric disorder:
17 Are the levels of psychiatric morbidity falling? *Psychological Medicine*
18 1995; 25:(2)277-83.
- 19 594. Harkki-Siren P, Sjoberg J, Makinen J *et al.* Finnish national register of
20 laparoscopic hysterectomies: a review and complications of 1165
21 operations. *American Journal of Obstetrics and Gynecology* 1997;
22 176:(1 Pt 1)118-22.
- 23 595. Hur M, Kim JH, Moon JS *et al.* Laparoscopically assisted vaginal
24 hysterectomy. *Journal of Reproductive Medicine* 1995; 40:(12)829-
25 33.
- 26 596. Johns DA and Diamond MP. Laparoscopically assisted vaginal
27 hysterectomy. *Journal of Reproductive Medicine* 1994; 39:(6)424-8.
- 28 597. Malzoni M, Perniola G, Perniola F *et al.* Optimizing the total
29 laparoscopic hysterectomy procedure for benign uterine pathology.
30 *Journal of the American Association of Gynecologic Laparoscopists*
31 2004; 11:(2)211-8.
- 32 598. Panici PB, Zullo MA, Angioli R *et al.* Minilaparotomy hysterectomy: a
33 valid option for the treatment of benign uterine pathologies. *European*
34 *Journal of Obstetrics, Gynecology, and Reproductive Biology* 2005;
35 119:(2)228-31.
- 36 599. Parkar RB, Thagana NG, and Otieno D. Laparoscopic assisted
37 vaginal hysterectomy for benign uterine pathology: is it time to
38 change? *East African Medical Journal* 2004; 81:(5)261-6.

- 1 600. Riza ED. Laparoscopically assisted vaginal hysterectomy: Report of
2 190 cases. *Journal of Laparoendoscopic and Advanced Surgical*
3 *Techniques* 1997; 7:(1)13-8.
- 4 601. Schofield MJ, Bennett A, Redman S *et al.* Self-reported long-term
5 outcomes of hysterectomy. *British Journal of Obstetrics and*
6 *Gynaecology* 1991; 98:(11)1129-36.
- 7 602. Takamizawa S, Minakami H, Usui R *et al.* Risk of complications and
8 uterine malignancies in women undergoing hysterectomy for
9 presumed benign leiomyomas. *Gynecologic and Obstetric*
10 *Investigation* 1999; 48:(3)193-6.
- 11 603. Toma A, Hopman WM, and Gorwill RH. Hysterectomy at a Canadian
12 tertiary care facility: Results of a one year retrospective review. *BMC*
13 *Women's Health* 2004; 4:(10)1-7.
- 14 604. Walker WJ and Barton-Smith P. Long-term follow up of uterine artery
15 embolisation - An effective alternative in the treatment of fibroids.
16 *BJOG: an International Journal of Obstetrics and Gynaecology* 2006;
17 113:(4)464-8.
- 18 605. Parker WH, Broder MS, Liu Z *et al.* Ovarian conservation at the time
19 of hysterectomy for benign disease. *Obstetrics and Gynecology* 2005;
20 106:(2)219-26.
- 21 606. Overton C and Maresh MJ. Audit of currently available endometrial
22 ablative techniques. *Baillieres Clinical Obstetrics and Gynaecology*
23 1995; 9:(2)357-72.

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1 **Evidence Tables**

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3 **[See separate file]**