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

Heavy menstrual bleeding

Clinical Guideline

January 2007

Funded to produce guidelines for the NHS by NICE

Update information
In March 2018 we updated and replaced this guideline with NICE guideline NG88 on heavy menstrual bleeding.

Some of the 2007 recommendations have been retained in the new guideline. This 2007 full guideline includes the evidence supporting the 2007 recommendations. Information that has been replaced by the new guideline has been shaded in grey.

For the current recommendations and updated evidence reviews, see the new guideline at http://www.nice.org.uk/guidance/ng88

Changes to NG88:
December 2024: We added links to relevant technology appraisal guidance in the section on management of HMB. This is to provide easy access to relevant guidance at the right point in the guideline only and is not a change in practice.

March 2020: In response to updated MHRA advice on the use of ulipristal acetate (Esmya) to say that healthcare professionals should contact patients currently taking Esmya for uterine fibroids as soon as possible and advise them to stop their treatment, we amended and withdrew recommendations. These recommendations may be reinstated or amended again at a later date depending on the outcome of the safety review now in progress.

These changes can be seen at http://www.nice.org.uk/guidance/NG88

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Commissioned by the National Institute for Health and Clinical Excellence

January 2007

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Contents

Guideline Development Group membership and acknowledgements

Guideline Development Group

GDG members

Mary Ann Lumsden	GDG Leader, Professor of Gynaecology
Anna-Marie Belli	Consultant Radiologist
Dianne Crowe	Gynaecology Specialist Nurse Practitioner
Sean Duffy	Clinical Director
Yasmin Gunaratnam	Patient/Carer Representative
Sarah Gray	General Practitioner
Klim McPherson	Visiting Professor of Public Health Epidemiology
David Parkin	Consultant Gynaecological Oncologist
Jane Preston	Consultant Obstetrician and Gynaecologist
Mark Shapley	General Practitioner
Bridgette York	Patient/Carer Representative

National Collaborating Centre for Women's and Children's Health (NCC-WCH) staff

Anna Bancsi	Work Programme Co-coordinator
Jiri Chard	Research Fellow
Martin Dougherty	Executive Director
Kate Homer	Information Officer
Irene Kwan	Research Fellow
Debbie Pledge	Information Specialist
Jeffrey Round	Health Economist
Hannah-Rose Douglas	Health Economist
Samantha Vahidi	Work Programme Co-coordinator
Martin Whittle	Clinical Co-director

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Additional support was received from Dr Francoise Cluzeau, Dr Ruth Garside, Professor Christine Lee, Dr Joanne Lord, Professor Rona McCandlish, Dr Margaret Rees, Mr Peter Reid, Dr Jeremy Wright, Dr Sian Jones and Dr Alfred Cutner. We also thank the Patient and Public Involvement Programme (PPIP) of the National Institute for Health and Clinical Excellence (NICE) whose glossary was adapted for use in this guideline.

Stakeholder organisations

Action and Support Group for Medical Victims of Richard Neale
Addenbrookes NHS Trust
Airedale General Hospital – Acute Trust
American Medical Systems UK
Anglesey Local Health Board
Association for Continence Advice
Association for Improvements in Maternity Services (AIMS)
Association of British Healthcare Industries

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Hospital Infection Society
Hysterectomy Association
Johnson & Johnson Medical
King's College Hospital NHS Trust
L'Arche UK
Leeds Teaching Hospitals NHS Trust
Liverpool Women's Hospital NHS Trust
London Fibroid Clinic
Luton and Dunstable Hospital NHS Trust
Maidstone and Tunbridge Wells NHS Trust
Maternity Health Links
Medicines and Healthcare products Regulatory Agency (MHRA)
Mental Health Foundation
Microsulis Medical Limited

Mid Staffordshire General Hospitals NHS Trust
National Association of Assistants in Surgical Practice
National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
National Endometriosis Society
National Osteoporosis Society
National Patient Safety Agency
National Public Health Service – Wales
NCCHTA
Newcastle PCT
NHS Direct
NHS Health and Social Care Information Centre
NHS Pathways
NHS Quality Improvement Scotland
North Eastern Derbyshire PCT
North Tees and Hartlepool NHS Trust
Northumbria Healthcare NHS Trust
Northwest London Hospitals NHS Trust
Nuffield Department of Obstetrics and Gynaecology, University of Oxford
Pelvic Pain Support Network
PERIGON (formerly The NHS Modernisation Agency)
Pfizer Ltd
Princess Alexandra Hospital NHS Trust
Queen Mary's Hospital NHS Trust (Sidcup)
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Rotherham Primary Care Trust
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Royal College of General Practitioners Wales
Royal College of Nursing
Royal College of Obstetricians and Gynaecologists
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Psychiatrists
Royal College of Radiologists
Royal Shrewsbury Hospital NHS Trust
Royal Society of Medicine
Royal Surrey County Hospital
Royal West Sussex Trust
Schering Health Care Ltd
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield South West Primary Care Trust
Sheffield Teaching Hospitals NHS Trust
Society and College of Radiographers
Society for Academic Primary Care
Society of Consultants and Lead Clinicians in Reproductive Health
South East Sheffield Primary Care Trust
Staffordshire Moorlans Primary Care Trust
Stockport PCT
Syner-Med
Tameside and Glossop Acute Services NHS Trust
UCLH NHS Foundation Trust
UK Anaemia
UK Specialised Services Public Health Network
University College London Hospitals NHS Trust
University Hospital Birmingham NHS Trust
Vitaline Pharmaceuticals UK Ltd
Welsh Assembly Government
Wirral Hospital NHS Trust
Women's Health Concern
Wyeth Laboratories

Abbreviations

AH	abdominal hysterectomy
AM	abdominal myomectomy
AUB	abnormal uterine bleeding
BSO	bilateral salpingo-oophorectomy
CI	confidence interval
COCs	combined oral contraceptives
DMPA	depot medroxyprogesterone acetate
DUB	dysfunctional uterine bleeding
EL	evidence level (level of evidence)
FSH	follicle-stimulating hormone
GDG	Guideline Development Group
GHQ	General Health Questionnaire
GnRH	gonadotrophin-releasing hormone
GPP	good practice point
HMB	heavy menstrual bleeding
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HTA	health technology appraisal
LAVH	laparoscopically assisted vaginal hysterectomy
LH	laparoscopic hysterectomy; luteinising hormone
LNG-IUS	levonorgestrel-releasing intrauterine system
LR	likelihood ratio
MBL	menstrual blood loss
MEA	microwave endometrial ablation
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PBAC	pictorial blood loss assessment chart
PCT	primary care trust
PPIP	Patient and Public Involvement Programme
PPV	positive predictive value
QALY	quality-adjusted life year
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
TLH	total laparoscopic hysterectomy
TVS	transvaginal ultrasound
UAE	uterine artery embolisation
VH	vaginal hysterectomy
vWD	von Willebrand disease
WMD	weighted mean difference

Glossary of terms

Abnormal uterine bleeding — Abnormal uterine bleeding can occur when a woman experiences a change in her menstrual loss, or the degree of loss or vaginal bleeding pattern differs from that experienced by the age-matched general female population.

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 does not. Bias can occur by chance or as a result of **systematic errors** in the design and execution of a study. Bias can occur at various stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples, see **selection bias**, **performance bias**, **information bias**, **confounder or confounding factor**, **publication bias**.

Bilateral salpingo-oophorectomy (BSO) — 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 **bias**. See also **double-blind study** and **single-blind study**.

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 **retrospective** as they look back in time from the outcome to the possible causes.

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

Case series — Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (**control**) group of patients.

Causal relationship — Describes the relationship between two **variables** 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 **randomised controlled trials** 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.
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 with 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 **focused question**.
Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses **controlled clinical trials** and **randomised controlled trials**.
Clinician	A healthcare professional providing patient care, e.g. doctor, nurse, physiotherapist.
Cluster	A group of patients, rather than an individual, used as the basic unit for investigation. See also **cluster design** and **cluster randomisation**.
Cluster design	Cluster designs are those where research subjects are not sampled or selected independently, but in a group. For example, a clinical trial where patients in a general practice are allocated to the same intervention; the general practice forming a cluster. See also **cluster** and **cluster randomisation**.
Cluster randomisation	A study in which groups of individuals (e.g. patients in a GP surgery or on a hospital ward) are randomly allocated to treatment groups. Take, for example, a smoking cessation study of two different interventions – leaflets and teaching sessions. Each GP surgery within the study would be randomly allocated to administer one of the two interventions. See also **cluster** and **cluster design**.

Cochrane Collaboration — An international organisation in which people find, appraise and review specific types of studies called **randomised controlled trials**. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the **Cochrane Library**.

Cochrane Library — The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of **randomised controlled trials** prepared by the **Cochrane Collaboration**). The Cochrane Library is available on CD-ROM and the internet.

Cognitive training — A 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 that did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or '**prospective**' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or '**retrospective**' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Co-morbidity — Coexistence 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 ten 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 **homogeneity**.

Control event rate — See **event rate**.

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

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

Cost–benefit analysis — A type of **economic evaluation** where both costs and benefits of healthcare 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 healthcare 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 analysis — A type of **economic evaluation** comparing the costs 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 **cost-effectiveness analysis** where health effects are measured in **quality-adjusted life years**. A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.

Counselling — Counselling is one of the professional psychological therapies that provides individuals and families/carers with an opportunity to explore emotional, physical and psychological difficulties that they may be experiencing and to help them resolve specific problems, make informed decisions, develop coping strategies and improve relationships with others.

Crossover study design — A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A,

	B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a **longitudinal study**, which follows a set of people over a period of time.)
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 should make decisions. There are several methods that decision analysts use to help people to make better decisions, including **decision trees**.
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 various 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 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 **consensus methods**.
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.
Discussion	Communication between a healthcare professional and a woman regarding a condition and its management. This is not the same as counselling, which is a therapeutic intervention.
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). The 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 **health economic** evaluations the consequences should include health outcomes.
Effectiveness	See **clinical effectiveness**.

Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared with 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 glandular inner layer of the uterus.
Epidemiology	The 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 **control** 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 level (EL)	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the **hierarchy of evidence** and how well it has adhered to recognised research principles. Also called **level of evidence**.
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 **selection criteria**.
Experimental event rate	See **event rate**.
Experimental study	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease – where the conditions of testing are to some extent under the control of the investigator. **Controlled clinical trials** and **randomised controlled trials** are examples of experimental studies.
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 **generalisability** 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 **qualitative research** technique. It is a method of group interview or discussion of 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. For example, do insulin pumps (intervention) improve blood sugar control (outcome) in adolescents with type 1 diabetes (population) compared with multiple insulin injections (comparison)? See also **clinical question**.
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 **heterogeneity** 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. **Publication bias** 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 **external validity**.
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 that 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.
Healthcare professional	A person who works within a health service but does not necessarily provide direct patient care, e.g. healthcare assistants.
Health economics	A branch of economics that studies decisions about the use and distribution of healthcare 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 **health technology**. 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 **homogeneity**. The term is used in **meta-analyses** and **systematic reviews** when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size

	of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of **variables** 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 **randomised controlled trials** (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs that 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 **systematic review** or **meta-analysis** are similar and there is no evidence of **heterogeneity**. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also **consistency**.
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.
Inclusion criteria	See **selection criteria**.
In-depth interview	A **qualitative research** technique. It is a face-to-face conversation between a researcher and a respondent with the purpose of exploring issues or topics in detail. It does not use pre-set questions, but is shaped by a defined set of topics or issues.
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 **blinding**), response errors (e.g. lack of **blinding** if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).
Intention-to-treat (ITT) 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). 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	See **evidence level**.
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 **cross-sectional study**, which observes a defined set of people at a single point in time.)

Masking — See **blinding**.

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 **systematic review** and **heterogeneity**.

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 **randomised controlled trial**, of 200 people, over 1 year.

Microwave endometrial ablation (MEA) — The MEA system is a surgical device that uses 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 cooperative study between different hospitals or an international collaboration involving patients from more than one country.

Myometrium — The muscular outer layer of the uterus.

Negative predictive value (NPV) — The proportion of people with a negative test result who do not have the disease (where not having the disease is indicated by the 'gold' standard test being negative).

Non-systematic review — See **review**.

Objective measure — A measurement that follows a standardised procedure that 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 others (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 (OR) — 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** and **risk ratio**.
Off label prescribing	When a drug or device is prescribed outside its **specific indication**, to treat a condition or disease for which it is not specifically licensed.
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.
Ovulation	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**.
Performance bias	Systematic differences in care provided apart from the intervention being evaluated. For example, if study participants know they are in the **control group** they may be more likely to use other forms of care, people who know they are in the experimental group may experience **placebo effects**, and care providers may treat patients differently according to which group they are in. Masking (**blinding**) of both the recipients and providers of care is used to protect against performance bias.
Pictorial blood loss assessment chart (PBAC)	A chart for recording the 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 that 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 placebo itself.

Positive predictive value (PPV) The proportion of people with a positive test result who have the disease (where having the disease is indicated by the 'gold' standard test being positive).

Power See **statistical power**.

Primary care Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.

Primary care trust (PCT) A primary care trust is an NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called **primary care**) and making sure that other appropriate health services are in place to meet local people's needs.

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 **co-morbidity**, that influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in **variables** (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 **confounding factors**. See also **prognostic marker**.

Prognostic marker A **prognostic factor** 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 **prognostic factors**. 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 that 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 that 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 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quantitative research Research that generates numerical data or data that can be converted into numbers, e.g. clinical trials or the national census that counts people and households.

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

Randomised controlled trial (RCT) A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups, with 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 (RR) A summary measure that 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 with 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 **prospective**.

Review A 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 **relative risk** is sometimes used as a synonym for risk ratio.

Rollerball endometrial ablation (REA) REA destroys the inner layers of the uterus using an 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 that usually combine an educational standards and examination role with the promotion of professional standards.
Saline infusion 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 injected. The saline fills and distends (expands) the endometrial cavity, providing visualisation 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 **sample** differ from those of the wider population from which the sample has been drawn or if 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, this 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.
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, this 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 an 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.
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 **methodological quality**.
Study type	The kind of design used for a study. **Randomised controlled trials**, **case–control studies** and **cohort studies** 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 **bias**.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a **meta-analysis**.
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 that 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)	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.
Transcervical resection of the endometrium (TCRE)	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 (TVS)	Transvaginal ultrasound is a method of imaging the genital tract in women. The ultrasound machine sends out high-frequency sound waves that 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 artery embolisation (UAE)	Uterine artery embolisation 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.
Uterine fibroids	Smooth-muscle tumours of the uterus, generally benign although occasionally (< 1%) malignant. They vary greatly 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 estrogen 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 **external validity** and **internal validity**.
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 that can be assessed or measured.

1 Introduction

Heavy menstrual bleeding (HMB) has an adverse effect on the quality of life of many women. It is not a problem associated with significant mortality. 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 treated successfully, it is essential that the underlying problem is understood by both the patient and the healthcare professional. This guideline provides 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 woman's and the healthcare professional's viewpoints and interests. This is not always easy but it is anticipated that the information contained in the guideline will help women reach an informed and beneficial decision with their doctors. Once they have read the guideline, they will know what questions to ask and what the options available to them are. Constructive dialogue should allow patients to be able to trust the advice given by their practitioner as they will be confident that they have the latest information and will be 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. This guideline has been developed with the aim of providing guidance on HMB. The effectiveness of the various treatments as well as their risks and benefits are discussed in relation to their use in the treatment of HMB but the discussion cannot be extrapolated to the use of particular treatments to relieve other symptoms, such as hysterectomy for cancer or endometriosis. The implications of each treatment in relation to fertility are also clearly stated so that no woman will undergo treatment that renders her infertile unless this is her specific wish.

Uterine fibroids are a common cause of HMB. The diagnosis and management are discussed in some depth although treatment for symptoms other than HMB is not included. The most up-to-date information is discussed so that the guideline will reflect current best practice. There are other gynaecological conditions such as adenomyosis or endometriosis where HMB may be associated with other menstrual symptoms as part of the presenting complaint. These conditions are excluded because HMB is not usually the principal presenting complaint and also because endometriosis could be the topic of a separate guideline.

In the early 1990s it was estimated that at least 60% of women presenting with HMB would have a hysterectomy to treat the problem, often as a first line. However, things have changed and the number of hysterectomies is decreasing rapidly. Hysterectomy is a major operation associated with significant complications in a minority of cases. It is also an emotive procedure: because the womb and fertility are often seen as being part of a woman's identity, the concept can be problematic and undesirable for some people. Nevertheless, clinically, hysterectomy is associated with a very high satisfaction rate by those who have undergone the operation. The high number of hysterectomies, the apparent lack of pathology and the lack of discussion of alternatives was a major cause for concern by professionals as well as the public. One of the principal aims of this guideline is to consider hysterectomy as well as the other treatment options and determine when they are likely to be the most appropriate for any particular individual.

Alternative effective treatments to hysterectomy are available for women with HMB, particularly for those who have a normal uterus and no significant pathology such as large uterine fibroids. As a result, the hysterectomies now performed tend to be more complicated than many of those in the past. This has significant implications for the acquisition and maintenance of surgical skills and this area is covered in some depth in this guideline. Surgical competence is an extremely important issue and recommendations are included as to how this might be made apparent to a patient. One possibility suggested is that details of the surgical practice of individual gynaecologists should be in the public domain.

It is often difficult for patients to appreciate that not all women are suitable for a particular new minimally invasive procedure. New therapies are often discussed in the media and this can give

patients hope that is, in some instances, inappropriate. This guideline aims to avoid this by including evidence-based and comprehensible discussions so that women can understand why doctors advise for or against a particular treatment. Doctors' decisions are informed by experience as well as by their knowledge of the evidence base. It is important that both are drawn upon in facilitating an open discussion with the patient. If the opinion of the doctor is contrary to that of the patient then a second opinion should be sought. This will mean that women will get the best possible advice and treatment.

1.1 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[1] This guideline provides advice on:

- patient educational interventions and information provision to improve patient satisfaction
- diagnosis of women presenting with HMB, including guidance on appropriate investigations and referral, and the cost-effectiveness of undertaking such investigations
- medical management of HMB, including short- and long-term outcomes, adverse events, cost-effectiveness and subsequent treatment
- indications for referral to secondary care management
- determining whether, and when, surgical procedures are most appropriate
- operative procedures used for endometrial ablation/resection in HMB, including short- and long-term outcomes, cost-effectiveness, adverse events and subsequent treatment
- uterine artery embolisation (UAE) in HMB, including short- and long-term outcomes, cost-effectiveness, adverse events and subsequent treatment
- operative procedures and other techniques used for hysterectomy and myomectomy in HMB, including short- and long-term outcomes, adverse events and subsequent treatment, as well as guidance on minimal access techniques (hysteroscopy or laparoscopy)
- issues relating to the removal of healthy ovaries, when hysterectomy is the most appropriate option
- the competencies required by practitioners who wish to carry out surgical techniques and other interventions such as UAE.

Advice on treatment options is based on the best evidence available to the Guideline Development Group. When referring to pharmacological interventions, the guideline normally recommends 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 assume that prescribers will use the Summary of Product Characteristics for prescribing decisions for individual women. The recommendations are based on the assessment of short- and long-term outcomes and complications for all treatments.

1.2 Areas outside of the remit of the guideline

This guideline does not address:

- conditions where HMB 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 HMB receiving exogenous steroids, such as hormone replacement therapy (HRT)
- gynaecological bleeding problems (other than HMB).

1.3 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, interventional radiologists, nurse practitioners, and general practitioners with a special interest in gynaecology.
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners and public health and trust managers
- women with HMB.

A version of this guideline for women, their families and the public can be downloaded from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/CG044publicinfo) or ordered from the NHS Response Line (0870 1555 455); quote reference number N1181.

1.4 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). The 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 a declaration form provided by NICE and are listed in Appendix D. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry.

1.5 Other relevant documents

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

- Guidelines:
  - *Osteoporosis: Assessment of Fracture Risk and Prevention of Osteoporotic Fracture in Individuals at High Risk* [under development]
  - *Referral Guidelines for Suspected Cancer*. CG026 (2005)
  - *Long-acting Reversible Contraception*. CG030 (2005).
- Technology appraisals:
  - *Fluid-filled Thermal Balloon and Microwave Endometrial Ablation Techniques for Heavy Menstrual Bleeding*. TA 78 (2004)
  - *Clinical Effectiveness and Cost Effectiveness of Technologies for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women* [TBC]
  - *Secondary Prevention of Osteoporotic Fractures in Post Menopausal Women* [TA 87; awaiting a response following appeal].
- Interventional procedures:
  - *Laparoscopic Hysterectomy* [in development]
  - *Laparoscopic Laser Myomectomy*. No. 23 (2003)
  - *Hysteroscopic Laser Myomectomy* [in development]
  - *Photodynamic Endometrial Ablation*. No. 47 (2004)
  - *Endometrial Cryotherapy for Menorrhagia*. No. 157 (2006).

1.6 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in the NICE technical manual.[2]

Literature search strategy

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

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

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

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were not applied to searches. Both generic and specially developed methodological search filters were used appropriately.

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

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

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

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

Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[2–9] and classified using the established hierarchical system shown in Table 1.1.[9] This system reflects the susceptibility to bias that is inherent in particular study designs.

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

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

Table 1.1 Levels of evidence for intervention studies

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

efficacy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was used.

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy for evidence of accuracy of diagnostic tests that takes into account the various factors likely to affect the validity of these studies (Table 1.2).[2]

For economic evaluations, no standard system of grading the quality of evidence exists. Economic evaluations that are included in the review have been assessed using a quality assessment checklist based on good practice in decision-analytic modelling.[10]

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

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

Table 1.2 Levels of evidence for studies of the accuracy of diagnostics tests

Level	Type of evidence
Ia	Systematic reviews (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; 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'

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

[b] 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.

[c] 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.

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

Health economics

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to HMB. The health economist helped the GDG by identifying topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where 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 1 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 1 corresponds to full health and a score of 0 corresponds to a health state equivalent to death. Negative valuations, implying a health state worse then 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 five to ten 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.[8] 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.

External review

This guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholder organisations the opportunity to comment on the scope of the guideline at the initial stage of development and on the evidence and recommendations at the concluding stage. The developers have carefully considered all of the comments during the consultation by registered stakeholders with validation by NICE.

Outcome measures used in the guideline

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

- change in menstrual blood loss (MBL)
- complications or adverse events associated with treatments
- change in health-related quality of life (HRQoL) measures.

Table 1.3 Classification of recommendations[8]

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

1.7 Schedule for updating the guideline

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

2 Summary of recommendations and care pathway

2.1 Key priorities for implementation (key recommendations)

Chapter 3 Impact of HMB on women

For clinical purposes, HMB should be defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms. Any interventions should aim to improve quality of life measures. [D]

Chapter 4 History taking, examination and investigations for HMB

If appropriate, a biopsy should be taken to exclude endometrial cancer or atypical hyperplasia. Indications for a biopsy include, for example, persistent intermenstrual bleeding, and in women aged 45 and over treatment failure or ineffective treatment. [D(GPP)]

Ultrasound is the first-line diagnostic tool for identifying structural abnormalities. [A]

Chapter 5 Education and information provision

A woman with HMB referred to specialist care should be given information before her outpatient appointment. The Institute's information for patients ('Understanding NICE guidance') is available from www.nice.org.uk/CG044publicinfo. [A]

Chapter 8 Pharmaceutical treatments for HMB

If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or non-hormonal treatments are acceptable, treatments should be considered in the following order:*

1. levonorgestrel-releasing intrauterine system (LNG-IUS) provided long-term (at least 12 months) use is anticipated†‡ [A]
2. tranexamic acid [A] or nonsteroidal anti-inflammatory drugs (NSAIDs) [A] or combined oral contraceptives (COCs) [B]
3. norethisterone (15 mg) daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestogens.§ [A]

* World Health Organization 'Pharmaceutical eligibility criteria for contraceptive use' (WHOMEC) apply. These criteria can be used to assess the individual's suitability for particular contraceptives. This allows informed decision making by the woman prior to the start of treatment. [www.ffprhc.org.uk/admin/uploads/298_UKMEC_200506.pdf]

† Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

‡ See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

§ Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented within the notes. In adolescents and women older than 40 years, refer to CSM advice issued in November 2004. Go to www.mhra.gov.uk and search for Depo Provera.

If hormonal treatments are not acceptable to the woman, then either tranexamic acid or NSAIDs can be used. [D(GPP)]

Chapter 10 Non-hysterectomy surgery for HMB

In women with HMB alone, with uterus no bigger than a 10 week pregnancy, endometrial ablation should be considered preferable to hysterectomy. [A]

Chapter 12 Hysterectomy

Taking into account the need for individual assessment, the route of hysterectomy should be considered in the following order: first line vaginal; second line abdominal. [A]

Chapter 14 Competencies

Maintenance of surgical, imaging or radiological skills requires a robust clinical governance framework including audit of numbers, decision making, case-mix issues and outcomes of all treatments at both individual operator and organisational levels. These data should be used to demonstrate good clinical practice. [D(GPP)]

2.2 Summary of recommendations

Chapter 3 Impact of HMB on women

Heavy menstrual bleeding (HMB) should be recognised as having a major impact on a woman's quality of life, and any intervention should aim to improve this rather than focusing on menstrual blood loss. [C]

For clinical purposes, HMB should be defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms. Any interventions should aim to improve quality of life measures. [D]

Chapter 4 History taking, examination and investigations for HMB

History

Initially, a history should be taken from the woman. This should cover the nature of the bleeding, related symptoms that might suggest structural or histological abnormality, impact on quality of life and other factors that may determine treatment options (such as presence of co-morbidity). [D(GPP)]

Clinicians should take into account the range and natural variability in menstrual cycles and blood loss when diagnosing HMB, and should discuss this variation with the woman. If the woman feels that she does not fall within the normal ranges, care options should be discussed. [D(GPP)]

If the history suggests HMB without structural or histological abnormality, pharmaceutical treatment can be started without carrying out a physical examination or other investigations at initial consultation in primary care, unless the treatment chosen is levonorgestrel-releasing intrauterine system (LNG-IUS). [D(GPP)]

If the history suggests HMB with structural or histological abnormality, with symptoms such as intermenstrual or post-coital bleeding, pelvic pain and/or pressure symptoms, a physical examination and/or other investigations (such as ultrasound) should be performed. [D(GPP)]

Measuring menstrual blood loss either directly (alkaline haematin) or indirectly ('pictorial blood loss assessment chart') is not routinely recommended for HMB. Whether menstrual blood loss is a problem should be determined not by measuring blood loss but by the woman herself. [D(GPP)]

Examination

A physical examination should be carried out before all:

- LNG-IUS fittings*
- investigations for structural abnormalities
- investigations for histological abnormalities. [D(GPP)]

Women with fibroids that are palpable abdominally or who have intra-cavity fibroids and/or whose uterine length as measured at ultrasound or hysteroscopy is greater than 12 cm should be offered immediate referral to a specialist. [D(GPP)]

Laboratory tests

A full blood count test should be carried out on all women with HMB. This should be done in parallel with any HMB treatment offered. [C]

Testing for coagulation disorders (for example, von Willebrand disease) should be considered in women who have had HMB since menarche and have personal or family history suggesting a coagulation disorder. [C]

A serum ferritin test should not routinely be carried out on women with HMB. [B]

Female hormone testing should not be carried out on women with HMB. [C]

Thyroid testing should only be carried out when other signs and symptoms of thyroid disease are present. [C]

Structural and histological abnormalities

If appropriate, a biopsy should be taken to exclude endometrial cancer or atypical hyperplasia. Indications for a biopsy include, for example, persistent intermenstrual bleeding, and in women aged 45 and over treatment failure or ineffective treatment. [D(GPP)]

Imaging should be undertaken in the following circumstances:

- the uterus is palpable abdominally
- vaginal examination reveals a pelvic mass of uncertain origin
- pharmaceutical treatment fails. [D(GPP)]

Ultrasound is the first-line diagnostic tool for identifying structural abnormalities. [A]

Hysteroscopy should be used as a diagnostic tool only when ultrasound results are inconclusive, for example, to determine the exact location of a fibroid or the exact nature of the abnormality. [A]

If imaging shows the presence of uterine fibroids then appropriate treatment should be planned based on size, number and location of the fibroids. [D(GPP)]

Saline infusion sonography should not be used as a first-line diagnostic tool. [A]

Magnetic resonance imaging (MRI) should not be used as a first-line diagnostic tool. [B]

Dilatation and curettage alone should not be used as a diagnostic tool. [B]

Where dilatation is required for non-hysteroscopic ablative procedures, hysteroscopy should be used immediately prior to the procedure to ensure correct placement of the device. [D(GPP)]

Chapter 5 Education and information provision

A woman with HMB referred to specialist care should be given information before her outpatient appointment. The Institute's information for patients ('Understanding NICE guidance') is available from www.nice.org.uk/CG044publicinfo. [A]

Although respect for autonomy, and individual choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost-effective. [D(GPP)]

* See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

Women should be made aware of the impact on fertility that any planned surgery or uterine artery embolisation (UAE) may have, and if a potential treatment (hysterectomy or ablation) involves the loss of fertility then opportunities for discussion should be made available. [D(GPP)]

Women should be given the following information on potential unwanted outcomes.

Table 5.1 Potential unwanted outcomes of interventions for HMB

Intervention	**Potential unwanted outcomes experienced by some women** (common = 1 in 100 chance, less common = 1 in 1000 chance, rare = 1 in 10 000 chance, very rare = 1 in 100 000 chance)	
Levonorgestrel-releasing intrauterine system (LNG-IUS)	Common:	irregular bleeding that may last for over 6 months; hormone-related problems such as breast tenderness, acne or headaches, which, if present, are generally minor and transient
	Less common:	amenorrhoea
	Rare:	uterine perforation at the time of IUS insertion
Tranexamic acid	Less common:	indigestion; diarrhoea; headaches
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Common:	indigestion; diarrhoea
	Rare:	worsening of asthma in sensitive individuals; peptic ulcers with possible bleeding and peritonitis
Combined oral contraceptives (COCs)	Common:	mood changes; headaches; nausea; fluid retention; breast tenderness
	Rare:	deep vein thrombosis; stroke; heart attacks
Oral progestogen (norethisterone)	Common:	weight gain; bloating; breast tenderness; headaches; acne (but all are usually minor and transient)
	Rare:	depression
Injected progestogen	Common:	weight gain; irregular bleeding; amenorrhoea; premenstrual-like syndrome (including bloating, fluid retention, breast tenderness)
	Less common:	small loss of bone mineral density, largely recovered when treatment is discontinued
Gonadotrophin-releasing hormone analogue (GnRH-a)	Common:	menopausal-like symptoms (such as hot flushes, increased sweating, vaginal dryness)
	Less common:	osteoporosis, particularly trabecular bone with longer than 6 months' use
Endometrial ablation	Common:	vaginal discharge; increased period pain or cramping (even if no further bleeding); need for additional surgery
	Less common:	infection
	Rare:	perforation (but very rare with second-generation techniques)

Table 5.1 (*cont.*)

Intervention	Potential unwanted outcomes experienced by some women (common = 1 in 100 chance, less common = 1 in 1000 chance, rare = 1 in 10 000 chance, very rare = 1 in 100 000 chance)	
Uterine artery embolisation (UAE)	Common:	persistent vaginal discharge; post-embolisation syndrome – pain, nausea, vomiting and fever (not involving hospitalisation)
	Less common:	need for additional surgery; premature ovarian failure, particularly in women over 45 years old; haematoma
	Rare:	haemorrhage; non-target embolisation causing tissue necrosis; infection causing septicaemia
Myomectomy	Less common:	adhesions (which may lead to pain and/or impaired fertility); need for additional surgery; recurrence of fibroids; perforation (hysteroscopic route); infection
	Rare:	haemorrhage
Hysterectomy	Common:	infection
	Less common:	intra-operative haemorrhage; damage to other abdominal organs, such as the urinary tract or bowel; urinary dysfunction – frequent passing of urine and incontinence
	Rare:	thrombosis (DVT and clot on the lung)
	Very rare:	death
	(Complications are more likely when hysterectomy is performed in the presence of fibroids)	
Oophorectomy at the time of hysterectomy	Common:	menopausal-like symptoms

Chapter 6 Choice

A woman with HMB should be given the opportunity to review and agree any treatment decision. She should have adequate time and support from healthcare professionals in the decision-making process. [D(GPP)]

A woman with HMB and/or her doctor should have the option of gaining a second medical opinion where agreement on treatment options for HMB is not reached. [D(GPP)]

Chapter 8 Pharmaceutical treatments for HMB

Pharmaceutical treatment should be considered where no structural or histological abnormality is present, or for fibroids less than 3 cm in diameter which are causing no distortion of the uterine cavity. [D(GPP)]

The healthcare professional should determine whether hormonal contraception is acceptable to the woman before recommending treatment (for example, she may wish to conceive). [D(GPP)]

If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or non-hormonal treatments are acceptable, treatments should be considered in the following order:*

1. levonorgestrel-releasing intrauterine system (LNG-IUS) provided long-term (at least 12 months) use is anticipated†‡ [A]
2. tranexamic acid [A] or nonsteroidal anti-inflammatory drugs (NSAIDs) [A] or combined oral contraceptives (COCs) [B]
3. norethisterone (15 mg) daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestogens.§ [A]

If hormonal treatments are not acceptable to the woman, then either tranexamic acid or NSAIDs can be used. [D(GPP)]

Women offered an LNG-IUS should be advised of anticipated changes in the bleeding pattern, particularly in the first few cycles and maybe lasting longer than 6 months. They should therefore be advised to persevere for at least 6 cycles to see the benefits of the treatment.¶ [D(GPP)]

If pharmaceutical treatment is required while investigations and definitive treatment are being organised, either tranexamic acid or NSAIDs should be used. [D(GPP)]

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

Ongoing use of NSAIDs and/or tranexamic acid is recommended for as long as they are found to be beneficial by the woman. [D(GPP)]

Use of NSAIDs and/or tranexamic acid should be stopped if it does not improve symptoms within three menstrual cycles. [D(GPP)]

When a first pharmaceutical treatment has proved ineffective, a second pharmaceutical treatment can be considered rather than immediate referral to surgery. [D]

Use of a gonadotrophin-releasing hormone analogue could be considered prior to surgery or when all other treatment options for uterine fibroids, including surgery or uterine artery embolisation (UAE), are contraindicated. If this treatment to be used for more than 6 months or if adverse effects are experienced then hormone replacement therapy (HRT) 'add-back' therapy is recommended.** [B]

Danazol should not be routinely used for the treatment of HMB. [A]

Oral progestogens given during the luteal phase only should not be used for the treatment of HMB. [A]

Etamsylate should not be used for the treatment of HMB. [A]

Chapter 10 Non-hysterectomy surgery for HMB

Endometrial ablation

Endometrial ablation should be considered where bleeding is having a severe impact on a woman's quality of life, and she does not want to conceive in the future. [C]

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* World Health Organization 'Pharmaceutical eligibility criteria for contraceptive use' (WHOMEC) apply. These criteria can be used to assess the individual's suitability for particular contraceptives. This allows informed decision making by the woman prior to the start of treatment. [www.ffprhc.org.uk/admin/uploads/298_UKMEC_200506.pdf]

† Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

‡ See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

§ Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented within the notes. In adolescents and women older than 40 years, refer to CSM advice issued in November 2004. Go to www.mhra.gov.uk and search for Depo Provera.

¶ See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

** Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

Endometrial ablation may be offered as an initial treatment for HMB after full discussion with the woman of the risks and benefits and of other treatment options. [A]

Women must be advised to avoid subsequent pregnancy and on the need to use effective contraception, if required, after endometrial ablation. [D(GPP)]

Endometrial ablation should be considered in women who have a normal uterus and also those with small uterine fibroids (less than 3 cm in diameter). [A]

In women with HMB alone, with uterus no bigger than a 10 week pregnancy, endometrial ablation should be considered preferable to hysterectomy. [A]

All women considering endometrial ablation should have access to a second-generation ablation technique. [D(GPP)]

Second-generation ablation techniques should be used where no structural or histological abnormality is present. [A] The second-generation techniques recommended for consideration are as follows. Providers should ensure that when purchasing any of these they buy the least expensive available option:*†‡§

- impedance-controlled bipolar radiofrequency ablation (formerly NICE interventional procedure guidance 104)
- fluid-filled thermal balloon endometrial ablation (TBEA) (formerly NICE interventional procedure guidance 6)
- microwave endometrial ablation (MEA) (formerly NICE interventional procedure guidance 7)
- free fluid thermal endometrial ablation (formerly NICE interventional procedure guidance 51).

In TBEA, endometrial thinning is not needed. [D(GPP)]

In MEA, scheduling of surgery for postmenstrual phase is an alternative to endometrial thinning. [A]

First-generation ablation techniques (for example, rollerball endometrial ablation (REA) and transcervical resection of the endometrium (TCRE)) are appropriate if hysteroscopic myomectomy is to be included in the procedure. [D(GPP)]

Dilatation and curettage

Dilatation and curettage should not be used as a therapeutic treatment. [C]

Chapter 11 Further interventions for uterine fibroids associated with HMB

For women with large fibroids and HMB, and other significant symptoms such as dysmenorrhoea or pressure symptoms, referral for consideration of surgery or uterine artery embolisation (UAE) as first-line treatment can be recommended.¶ [D(GPP)]

UAE, myomectomy or hysterectomy should be considered in cases of HMB where large fibroids (greater than 3 cm in diameter) are present and bleeding is having a severe impact on a woman's quality of life. [C]

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

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

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* NICE have produced 'Fluid-filled thermal balloon and microwave endometrial techniques for heavy menstrual bleeding. NICE technology appraisal guidance 78' on TBEA and MEA.

† This clinical guideline supersedes the following NICE interventional procedure guidances: 'Balloon thermal endometrial ablation. IPG 6', 'Microwave endometrial ablation. IPG 7', 'Free fluid endometrial ablation. IPG 51' and 'Impedance-controlled bipolar radiofrequency ablation for menorrhagia. IPG 104'. However, 'Endometrial cryotherapy for menorrhagia. NICE interventional procedure guidance 157' is not covered by this guideline.

‡ Reference should be made to the limits on uterus size given by the manufacturer of the endometrial ablation device.

§ 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').

¶ See 'Uterine artery embolisation for the treatment of fibroids', NICE interventional procedure guidance 94, www.nice.org.uk/IPG094.

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

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

Prior to scheduling of UAE or myomectomy, the uterus and fibroid(s) should be assessed by ultrasound. If further information about fibroid position, size, number and vascularity is required, MRI should be considered. [D(GPP)]

Pre-treatment before hysterectomy and myomectomy with a gonadotrophin-releasing hormone analogue for 3 to 4 months should be considered where uterine fibroids are causing an enlarged or distorted uterus.† [A]

If a woman is being treated with gonadotrophin-releasing hormone analogue and UAE is then planned, the gonadotrophin-releasing hormone analogue should be stopped as soon as UAE has been scheduled. [D(GPP)]

Chapter 12 Hysterectomy

Hysterectomy should not be used as a first-line treatment solely for HMB. Hysterectomy should be considered only when:

- other treatment options have failed, are contraindicated or are declined by the woman
- there is a wish for amenorrhoea
- the woman (who has been fully informed) requests it
- the woman no longer wishes to retain her uterus and fertility. [C]

Women offered hysterectomy should have a full discussion of the implication of the surgery before a decision is made. The discussion should include: sexual feelings, fertility impact, bladder function, need for further treatment, treatment complications, the woman's expectations, alternative surgery and psychological impact. [D(GPP)]

Women offered hysterectomy should be informed about the increased risk of serious complications (such as intraoperative haemorrhage or damage to other abdominal organs) associated with hysterectomy when uterine fibroids are present. [C]

Women should be informed about the risk of possible loss of ovarian function and its consequences, even if their ovaries are retained during hysterectomy. [D(GPP)]

Individual assessment is essential when deciding route of hysterectomy. The following factors need to be taken into account:

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

Taking into account the need for individual assessment, the route of hysterectomy should be considered in the following order: first line vaginal; second line abdominal. [A]

Under circumstances such as morbid obesity or the need for oophorectomy during vaginal hysterectomy, the laparoscopic approach should be considered, and appropriate expertise sought. [D(GPP)]

When abdominal hysterectomy is decided upon then both the total method (removal of the uterus and the cervix) and subtotal method (removal of the uterus and preservation of the cervix) should be discussed with the woman. D[(GPP)]

* See 'Uterine artery embolisation for the treatment of fibroids', NICE interventional procedure guidance 94, www.nice.org.uk/IPG094.

† Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

Chapter 13 Removal of ovaries at the time of hysterectomy

Removal of healthy ovaries at the time of hysterectomy should not be undertaken. [D(GPP)]

Removal of ovaries should only be undertaken with the express wish and consent of the woman. [D(GPP)]

Women with a significant family history of breast or ovarian cancer should be referred for genetic counselling prior to a decision about oophorectomy.* [D(GPP)]

In women under 45 considering hysterectomy for HMB with other symptoms that may be related to ovarian dysfunction (for example, premenstrual syndrome), a trial of pharmaceutical ovarian suppression for at least 3 months should be used as a guide to the need for oophorectomy. [D(GPP)]

If removal of ovaries is being considered, the impact of this on the woman's wellbeing and, for example, the possible need for hormone replacement therapy (HRT) should be discussed. [D(GPP)]

Women considering bilateral oophorectomy should be informed about the impact of this treatment on the risk of ovarian and breast cancer. [D(GPP)]

Chapter 14 Competencies

Training

All those involved in undertaking surgical or radiological procedures to diagnose and treat HMB should demonstrate competence (including both technical and consultation skills) either during their training or in their subsequent practice. [D(GPP)]

The operative competence of healthcare professionals who are acquiring new skills in 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 and Training Board (PMETB), the Royal Colleges and/or the Society and College of Radiographers (SCoR). [D(GPP)]

Training programmes must be long enough to enable healthcare professionals to achieve competency in complex procedures when these are appropriate (for example, operations for fibroids that are large or in an awkward position, or using laparoscopic techniques). These training programmes will usually be located in units with a particular interest and sufficient workload to allow experience of these procedures. [D(GPP)]

Maintenance

Maintenance of surgical, imaging or radiological skills requires a robust clinical governance framework including audit of numbers, decision making, case-mix issues and outcomes of all treatments at both individual operator and organisational levels. These data should be used to demonstrate good clinical practice. [D(GPP)]

Established healthcare professionals should be able to demonstrate that their training, experience and current practice meets or exceeds the standards laid out for newly trained professionals. [D(GPP)]

Governance

If a healthcare professional lacks competence to undertake a procedure then they should refer the woman to a professional with the appropriate skill. Organisations that commission services should be responsible (through service specification based on robust audit data) for identifying and contracting professionals with appropriate skills. [D(GPP)]

* See 'The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care', NICE clinical guideline 41, www.nice.org.uk/CG041, for more detail.

2.3 Research recommendations

Chapter 3 Impact of HMB on women

Risk factors for HMB and uterine pathology

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

Impact of HMB on quality of life

- The currently available HMB-specific HRQoL 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.

Chapter 4 History taking, examination and investigations for HMB

Measurement of menstrual blood loss

- Investigate routine use of indirect measurements of menstrual blood loss 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.

Chapter 8 Pharmaceutical treatments for HMB

- A study to investigate the use of LNG-IUS in fibroids greater than 3 cm.
- A study to examine the association between size and site of uterine fibroids and HMB.

Chapter 10 Non-hysterectomy surgery for HMB

Endometrial ablation

- Where evidence is not available on endometrial thinning prior to different ablative techniques, it is recommended this research be undertaken.
- An RCT investigation of the clinical effectiveness and cost-effectiveness of the various second-generation ablation techniques against one another.
- An opportunity to evaluate any new endometrial ablation techniques within an RCT format.

Chapter 11 Further interventions for uterine fibroids associated with HMB

- What effect do UAE and myomectomy have on the long-term fertility of women?
- What are the psychosexual impacts of UAE and myomectomy?
- What are the long-term recurrence rates of fibroids after UAE or myomectomy?
- How does UAE affect 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?

Chapter 12 Hysterectomy

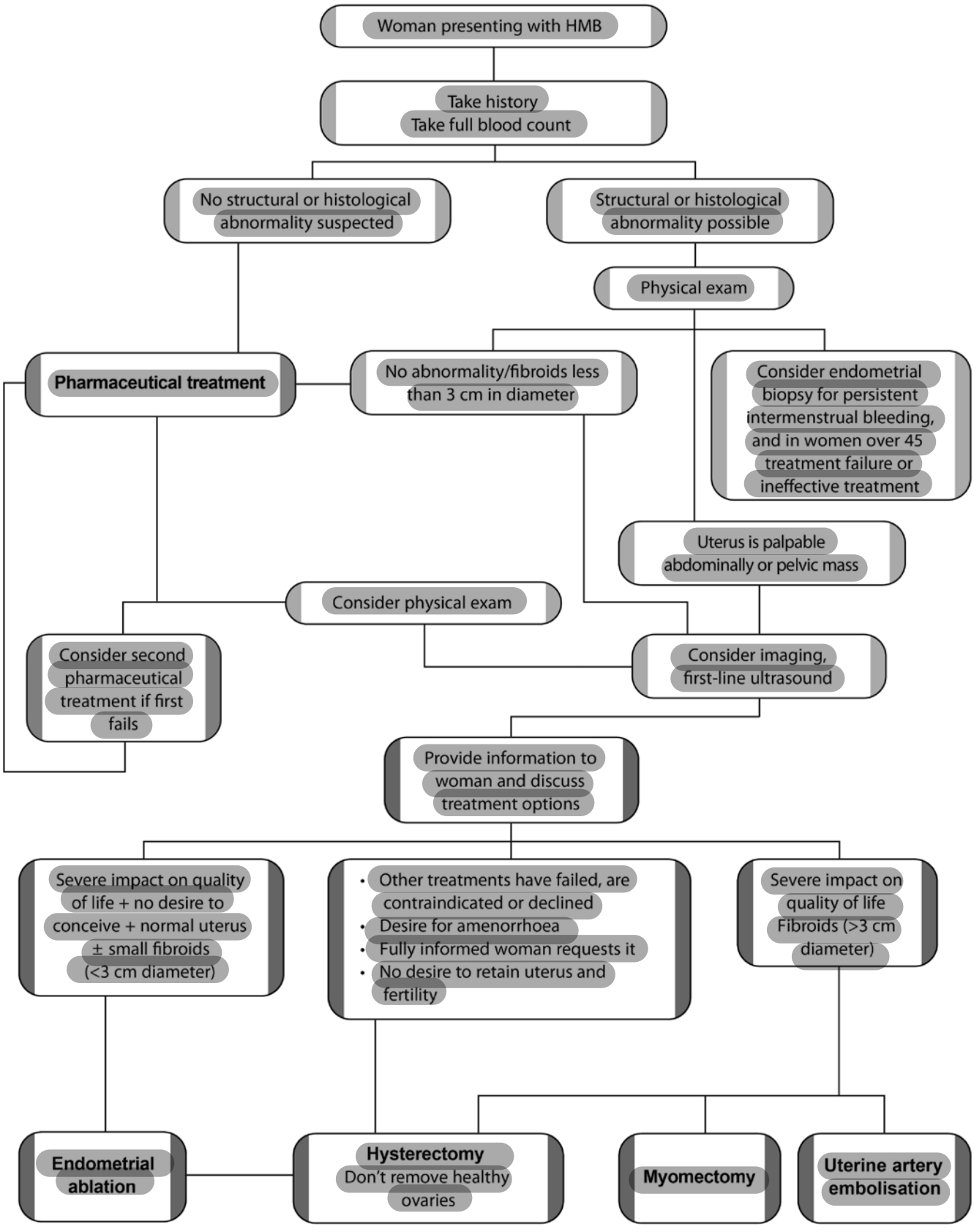
- An investigation into the medium- and long-term outcomes of sub-total and total hysterectomy.
- An investigation into the effect of hysterectomy and oophorectomy on cancer.

Chapter 14 Competencies

- Do volume–outcome relationships exist in gynaecological procedures, taking into account case-mix, hospital and surgeon factors?

2.4 Care pathway

The care pathway shown opposite is taken from the NICE Quick Reference Guide version of this guideline (www.nice.org/uk/CG044).


Woman presenting with HMB
Take history
Take full blood count
No structural or histological abnormality suspected
Structural or histological abnormality possible
Physical exam
Pharmaceutical treatment
No abnormality/fibroids less than 3 cm in diameter
Consider endometrial biopsy for persistent intermenstrual bleeding, and in women over 45 treatment failure or ineffective treatment
Uterus is palpable abdominally or pelvic mass
Consider physical exam
Consider second pharmaceutical treatment if first fails
Consider imaging, first-line ultrasound
Provide information to woman and discuss treatment options
Severe impact on quality of life + no desire to conceive + normal uterus ± small fibroids (<3 cm diameter)
• Other treatments have failed, are contraindicated or declined
• Desire for amenorrhoea
• Fully informed woman requests it
• No desire to retain uterus and fertility
Severe impact on quality of life Fibroids (>3 cm diameter)
Endometrial ablation
Hysterectomy
Don't remove healthy ovaries
Myomectomy
Uterine artery embolisation

3 Impact of HMB on women

3.1 Defining HMB

3.1.1 What is menstruation?

Menstruation is a woman's monthly bleeding from the reproductive (vaginal) 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.

3.1.2 'Normal' menstrual patterns

'Normal' menstrual patterns and blood loss

Beliefs derived from personal experience and cultural, social and educational influences give rise to a sense of what 'normal' blood loss is during a menstrual period 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.[11] 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 (MBL).

The 'normal' quantity of MBL can be defined based on the distribution of objectively measured MBL for the whole population. However, the distribution of 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. Studies have thus been undertaken that examine changes in blood chemistry that are known to have a relationship with blood loss and sense of wellbeing.

3.1.3 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 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 1–19 days (median of 5 days), with 97% lasting 3–8 days.[12] [EL = 3]

A study ($n = 1472$) examined menstrual histories of adolescent girls aged 11–15 years. The study found the duration of menstruation in 89% of girls was 3–7 days.[13] [EL = 3]

A study ($n = 2700$) assessed menstrual histories of women of all ages. The study found the mean duration of menstruation changed from 3.9 days at age 20 years to 2.8 days at age 40 years.[14] [EL = 3]

A study assessed menstrual histories ($n = 31\,593$ menstrual cycles) of women of all ages. The study found the mean duration of menstruation was 4.7 days in women aged 13–17 years and 4.1 days in women aged over 40 years.[15] [EL = 3]

Normal cycle length

Five studies reported length of menstrual cycles, with three reporting a mean of 28 days and one reporting a mean of 30 days. Three smaller studies also reported figures.[14–21] However, as many authors note, these figures are crude and the use of mean is questionable given the skewed distribution of figures.

Several studies identified a relationship between cycle length and age.

A study ($n = 2865$) examined menstrual histories to assess menstrual cycle length. The study found that for ages 15–19 years the mean cycle length was 28.8 days (SD 2.9), compared with 27.5 days (SD 2.4) in women aged 35–44 years.[22] [EL = 3]

A study ($n = 2316$) used menstrual histories to examine whether menstrual cycle length was related to age. The study found that for ages 15–19 years the mean cycle length was 30.8 days (SD 3.4), with 68.4% in the 25–31 day range. By 35–39 years of age the mean cycle length was 28.5 days (SD 2.6), with 86.4% in the 25–31 day range.[23] [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 of 34.7 days (10th to 90th percentile = 28–44 days) for ages 13–17 years, to a mean of 28.4 days (10th to 90th percentile = 25–32 days) for ages 40–52 years.[15] [EL = 3]

Five studies provided data on regularity of menstrual cycles.[14,15,18,22,24] In one survey study ($n = 2865$) that examined menstrual cycle characteristics, the level of irregular periods reduced with age, from 20.8% for ages 15–19 years, to 10.8% for ages 40–44 years.[22] [EL = 3] Two studies recorded the variation within women between cycles.[15,24] 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 the distribution of MBL for the whole population. However, this does not relate to the physiological impact of MBL. Studies have thus been undertaken that examine changes in blood chemistry (that are felt to be correlated with a sense of wellbeing) and 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 found that haemoglobin and ferritin levels adversely changed at MBL levels of 76.4 ml. As a result, the study found the upper limit of the mean as being between 60 and 80 ml MBL (these figures were based on a defined subgroup that excluded women with existing menstrual problems).[25] [EL = 3]

A study ($n = 313$) on women used blood tests to examine the impact of MBL on overall blood chemistry. It found that anaemia and iron depletion occurred at two points, first at around 60 ml MBL and then at around 120 ml MBL. The study concluded that a definition of around 120 ml may be more useful for the treatment of HMB as this was when anaemia was most likely to occur.[26] [EL = 3]

A study ($n = 348$) used blood tests to assess whether changes in overall blood chemistry were associated with MBL. The study defined heavy bleeding as ≥ 45 ml but this was based on dividing the study population into equal percentile groups, rather than biological factors. This study also found that MBL varied between cycles within the same women, with 40% of women having a 10 ml difference between cycles.[27] [EL = 3]

3.1.4 Evidence statements on 'normal' menstrual patterns

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

3.1.5 GDG interpretation of evidence on 'normal' menstrual patterns

The GDG agreed that the findings of the research provided a valid picture of the epidemiology in the general population and the physiological background to HMB.

The GDG felt that the natural variability in length of cycle meant that defining HMB as regular could be counterproductive to the management of the condition.

The GDG highlighted that recognition of the variability of menstrual cycles and blood loss that occurs within the general population of women, and is experienced by an individual woman, is important when determining clinical care.

Research recommendations on defining 'normal' menstrual patterns

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

3.2 Risk factors for increased menstrual bleeding

While 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. Further detail is contained in evidence tables 3.1 to 3.3.

3.2.1 Review of risk factors associated with HMB

Overview of available evidence
In total, 28 studies were included that assessed risk factors associated with HMB.

Uterine fibroids
Uterine fibroids are a commonly occurring pathology,[28] and are age related.[29–31] Studies have also shown that uterine fibroids are more common in Afro-Caribbean women than in white women ($P = 0.001$).[32]

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 > 5 cm = 2.4).[33] [EL = 2+]

One epidemiological study ($n = 50$) undertaken in the UK on women with uterine fibroids assessed the association with MBL. The study found that site, size and number of fibroids are linked to the level of MBL.[34] [EL = 3]

Three observational studies found that uterine fibroids are associated with menorrhagia (with rates between 27% and 54%).[35–37] However, one diagnostic study found that fibroids were not a common cause of adolescent menorrhagia.[38]

Age
Eleven observational studies examined the relationship between MBL and age.[15,25,27,39–46]

One study from Sweden examined the use of the alkaline haematin test to measure menstrual patterns. The study ($n = 476$) found a rise from 33.8 ml at age 15 years to a peak of 49.7 ml at 30 years, before falling back to 42.7 ml at 45 years.[25] [EL = 3] Studies using subjective measures also found an increase in MBL with age.[27] One study found that MBL increased with age ($P = 0.002$) (46.8% of women aged 18–24 years and 53.0% of those aged 45–54 years reported HMB).[41] However, three studies found no association between age and MBL.[44–46]

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

Blood disorders
One systematic review and two observational studies found that inherited blood disorders, such as von Willebrand disease (vWD), are associated with higher MBL, with a vWD prevalence of

13.0–15.4% in women with menorrhagia[47–49] [EL = 2+; EL = 2–; EL = 3] compared with the general population.[50] [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 with women without menorrhagia was 8.6 (95% CI 1.3 to 194.6).[51] [EL = 2+]

Thyroid disorders

One study ($n = 428$) found no association between thyroid disorders and the presence of bleeding disorders.[52] [EL = 2+]

Endometriosis/adenomyosis

The main presenting symptom for endometriosis is usually dysmenorrhoea but two studies have found that HMB may be a significant secondary symptom. One observational study ($n = 315$) found that endometriosis was associated with higher pictorial blood loss assessment chart (PBAC) scores (110 versus 84, $P = 0.007$), when compared with a non-endometriosis group.[53] [EL = 2–] One study ($n = 215$) found that 73% of women with endometriosis have a history of menorrhagia.[54] [EL = 3] One retrospective study ($n = 1542$) on results of pathology tests found that, of 134 women with dysfunctional uterine bleeding (DUB), 33 had endometriosis.[55] [EL = 3]

Racial group

Four observational studies from the USA and Egypt found some association between racial group and MBL,[44,45,56,57] with one study finding an OR of 4.99 (95% CI 2.07 to 12.05) for hypermenorrhoea in non-Caucasians compared with Caucasians. However, this study did not allow for prevalence of underlying conditions[56] and the division of the study groups into broad racial (and not ethnic) categories does not enable examination of the relationships between ethnicity and HMB that are relevant to the increasing ethnic diversity of the UK population.

Ethnic or cultural group

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

Parity

Two observational studies ($n = 344$; $n = 774$) found a small association between number of pregnancies and MBL.[45,58] [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.[43] [EL = 3]

Lifestyle

Three observational studies have found that lifestyle may impact on MBL. One study ($n = 2912$) found that among US naval personnel self-reported MBL was increased by smoking (OR 1.17, $P < 0.001$) and high alcohol consumption (OR 1.4, $P < 0.05$).[44] [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 with controls not doing so.[59] [EL = 2–] One study ($n = 2663$) found that weight may be an issue.[60] (EL = 3] 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.[61–63] It is not known in

community populations whether increased MBL causes mental/emotional problems or whether mental/emotional problems increase the reporting of HMB, or both. One study has suggested that in some women psychological distress occurs before the reporting of menorrhagia.[62]

One cohort study ($n = 1517$) from the UK, on women aged between 20 and 59 years, examined the association of menstrual and mental health problems. The study found that when the women were asked to assess their MBL, 19.0% said it was light, 51.3% moderate, 24.3% heavy and 5.4% very heavy. The study found an association between classification of depression (GHQ of >12) and MBL level ($x^2 = 20.11$, $P = 0.0002$).[61] [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 quality of life. The study found evidence that the impact of HMB on health-related quality of life (HRQoL) was related to the level of medical attention that women accessed.[62] [EL = 2–]

A case–control study ($n = 645$) compared the HRQoL of women consulting for HMB with that of 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 versus consulting controls OR 1.26 (95% CI 0.74 to 2.13) or between consulting versus non-consulting controls OR 1.43 (95% CI 0.85 to 2.38).[63] [EL = 2+]

In women consulting primary care for HMB, studies have found that psychological distress is not a predictor for future consultation[64] 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.[63] The main motivation for consultation was interference in life from heavy periods. Studies also found no difference in the presence of a past psychiatric disorder compared with women consulting with an illness other than HMB.[62] 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.[65,66] [EL = 2–; EL = 2–] However, two studies ($n = 50$; $n = 44$) found that higher MBL was associated with worse mental health scores, although there was no control for consultation behaviour.[67,68] [EL = 2–; EL = 2+]

3.2.2 Evidence statements 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 wellbeing 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.

3.2.3 GDG interpretation of evidence on risk factors for HMB

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

3.3 Prevalence of uterine pathology

Studies on populations of women with 'normal' menstrual patterns indicate that variability and change in MBL are common. However, 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.

3.3.1 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 abnormal uterine bleeding (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.[37] [EL = 3]

A diagnostic randomised controlled trial (RCT) ($n = 683$) undertaken in the UK on women with AUB was identified. From the figures for levels of pathology identified, it was possible to calculate basic prevalence levels. In a moderate-risk group (premenopausal, >40 years old) it was found that 11.5% had endometrial/uterine polyps, 36% had uterine fibroids, 1% had endometrial cancer and 1% had hyperplasia. For the low-risk group (premenopausal, < 40 years old, no other risk factors), 6% had endometrial/uterine polyps, 19% had uterine fibroids, none had endometrial cancer and none had hyperplasia. The high-risk group covered postmenopausal women and is thus not shown here.[69] [EL = Ib]

A diagnostic study ($n = 793$) undertaken in Italy involving women with menorrhagia examined the use of hysteroscopy and ultrasonography to assess uterine pathology. The study reported that 325 had normal findings and 445 had abnormal findings: 234 (29.5%) with submucous myomas, 155 (19.5%) with endometrial polyps, 76 (9.5%) with endometrial hyperplasia (of any type) and 2 (0.2%) with endometrial carcinoma.[70] [EL = II]

A diagnostic study ($n = 2500$) undertaken in the UK on women referred for hysteroscopy reported the following diagnostic findings in 1120 women referred with menorrhagia: 583 (52.1%) had normal results, 334 (29.8%) had uterine fibroids, 112 (10.0%) had polyps, 8 (0.7%) had atrophy, 29 (2.6%) had irregular endometrium, 3 (0.3%) had endometrial carcinoma and 51 (4.6%) were classified as miscellaneous.[71] [EL = II]

A case series of women ($n = 1029$) from the UK who had undergone diagnostic dilatation and curettage found that 281 (27.4%) of the women had 'failed' (procedure not complete or no suitable material retrieved), 627 (60.9%) had normal results, 57 (5.5%) had unspecified hyperplasia, 8 (0.8%) had endometriosis, 21 (2.0%) had endometrial polyps, 15 (1.4%) had endometrial carcinoma, 8 (0.8%) had atrophic endometrium and 12 (1.2%) had others conditions. However, this study was not specifically on women with menstrual problems, so results have to be extrapolated.[72] [EL = III]

A retrospective case series ($n = 139$) from Switzerland of women with AUB examined the diagnostic use of histopathological analysis. The results showed that 33 (24%) of the women had polyps, 22 (16%) had submucous fibroids and 5 (3.6%) had endometrial hyperplasia.[73] [EL = II]

A diagnostic study ($n = 419$) undertaken in the USA on premenopausal women examining the use of hysteroscopy, dilatation and curettage or biopsy for identification of uterine pathology was identified. The study found that, of 415 women examined, 165 (39%) had endometrial polyps, 68 (16%) had submucous leiomyomas and 16 (8.5%) had adenomatous hyperplasia. However, this study was not specifically focused on women with menstrual problems.[74] [EL = II]

A case series ($n = 2581$) undertaken in the UK of women with menstrual problems examining the use of hysteroscopy for identification of uterine pathology was identified. The study found that 11.4% had submucous fibroids, 10.6% had polyps and 1.6% had endocervical polyps. The study assessed differences between premenopausal and postmenopausal women and found that 22% of postmenopausal versus 3.4% of premenopausal women had hyperplasia (of any type). The study also found that submucous fibroids were more common in premenopause than in postmenopause (11.8% versus 10.7%, $P = 0.43$) and that polyps were more common in postmenopause than in premenopause (13.9% versus 8.9%, $P = 0.0001$).[75] [EL = III]

A case series of women ($n = 215$) diagnosed with endometritis found that 76% had a history of menorrhagia.[54] [EL = 2–]

A diagnostic study ($n = 275$) on women with AUB found a prevalence of endometriosis of between 18.3% and 15.4% in the two groups studied.[76] (EL = Ia]

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.[77] [EL = III]

A diagnostic study ($n = 43$) undertaken in Italy on women with menorrhagia compared ultrasound with histology techniques. The study found that 46.5% had histopathology-confirmed adenomyosis.[78] [EL = II]

A diagnostic study ($n = 102$) undertaken in Italy on women with menorrhagia compared results from ultrasound with those from endometrial biopsy. The study found that the prevalence of adenomyosis was 28%.[79] [EL = Ib]

A cohort study ($n = 180$) compared prevalence of pathology in women with and without AUB. The study found a higher rate of pathology in women with AUB ($P < 0.05$).[80] [EL = 2+]

A diagnostic study ($n = 370$) in a group of women with AUB referred for hysteroscopy found that 33.5% had a normal cavity and the rest had some form of pathology. However, these findings are from a highly selected secondary care group.[81] [EL = II]

A retrospective case series ($n = 3241$) of women with menorrhagia referred for investigation for endometrial cancer found no cases reported.[82] [EL = 3]

A retrospective case series ($n = 1033$) of women with heavy or irregular bleeding referred for investigation found that five had endometrial cancer and 45 had hyperplasia. The risk factors associated with cancer were weight, family history, age and infertility.[83] [EL = 3]

A diagnostic study ($n = 187$) on women with AUB found the following pathology among women with menorrhagia: 68 had normal pathology, 13 had polyps, 16 had fibroids, 3 had hyperplasia and 2 had endometriosis.[84] [EL = II]

A retrospective case series ($n = 665$) identified that uterine pathology was more likely in women aged over 40 years compared with those under 40 years (32% versus 21%).[85] [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 the ovary and 9 had carcinoma.[86] [EL = 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 and Wales is given in Table 3.1, which shows an age-related increase.

Table 3.1 Endometrial cancer incidence by age per 100 000; data from the Office for National Statistics[87]

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

The data for lifetime risk of endometrial cancer reinforce the incidence findings. The lifetime risk of endometrial cancer for women at various ages in the USA and in Scotland (figures not available for women aged under 64 years) are shown in Tables 3.2 and 3.3, respectively. The figures for Scotland show a lower rate of endometrial cancer in than in the USA.

Table 3.2 Lifetime risk of endometrial cancer in the USA; data from NOS Cancer by Race, Females SEER 17 Registries for 2000–2002)[88]

Age (years)	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

Table 3.3 Lifetime risk of endometrial cancer in Scotland; data (extracted October 2004) from Scottish Cancer Registry[89]

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

Note that the sentence

'This was based on the incidence of endometrial carcinoma of 38% in women with HMB'

should read:

'This was based on the incidence of HMB of 38% in women with endometrial carcinoma'

However, this does not show the incidence and risk among women with HMB. The RCOG guidelines on HMB estimated that in women aged between 35 and 54 years, eight of every 10 000 women who presented with HMB in primary care would have endometrial carcinoma.[90] This was based on the incidence of endometrial carcinoma of 38% in women with HMB, the 1987 incidence of cancer and the frequency of consultation in primary care with HMB of 5%. These figures have been updated with 2003 data (the latest available). In women aged under 30 years the estimate is less than 0.01% or 1 per 10 000 consultations for HMB in primary care. The likely rates of endometrial carcinoma per 10 000 consultations for HMB in primary care for older age groups are given in Table 3.4.

Table 3.4 Likely rates of endometrial cancer per 10 000 consultations for HMB in primary care

Age range (years)	30–34	35–39	40–44	45–49
Rate of endometrial cancer per 10 000 consultations	1	1	3	8

These figures probably overestimate the incidence in the HMB population, as the prevalence figures are based on women with endometrial carcinoma reporting HMB rather than women with HMB having endometrial cancer, which would be a more relevant measure. One study from a secondary care setting found that, of 987 women with confirmed menorrhagia, 5 (0.5%) had endometrial cancer, and a further 45 (4.5%) had hyperplasia.[83] If these figures are used instead of the 38% previously used then the rates per 10 000 would be all be less than 1. Indeed, there is no clear data linking HMB to endometrial cancer, with most studies concentrating on irregular bleeding[91,91–93] or not assessing menstrual symptoms.[94]

In addition, NICE has produced guidelines for the referral of women with suspected malignancy from primary care, and concluded that this is necessary in women with persistent intermenstrual bleeding. This implies that women with a normal pelvic examination and/or other symptoms of vaginal bleeding do not require investigation or referral from primary care.[95]

3.3.2 Evidence statements on uterine pathology

The results of 20 observational and diagnostic studies show that the majority of women with HMB have no histological abnormality that can be implicated in causing HMB. Uterine fibroids (approximately 30% of women) and polyps (approximately 10% of women) are the most common form of pathology found. It is rare for a woman who has presented with HMB and has undergone investigations to have an underlying pre-malignant or malignant condition. However, there is a lack of research on the prevalence of significant uterine pathology in primary care populations, which hinders the production of predictive values for use in primary care.

3.3.3 GDG interpretation of evidence of uterine pathology

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

The GDG highlighted that the assessment of hyperplasia now focuses on differentiating between normal and atypical types, as atypical hyperplasia has been shown to be closely linked to the development of future malignancy.

3.4 Impact of HMB on quality of life

A basic reason for people seeking help for a health condition is the perceived impact it is having on their health-related quality of life (HRQoL) 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 HRQoL.

3.4.1 Review of impact of HMB on quality of life

Quality of life measures for women with HMB

One systematic review found limited use of HRQoL measures, mainly SF-36. However, there is no specific HRQoL measure for HMB.[96] [EL = 2++]

Four studies have examined the use of general HRQoL measures in HMB.[97–100] One study examined the use of SF-36. Of eight scales in SF-36, two (mental health and general health perceptions) had lower internal reliability when assessed in women with HMB compared with the general population (0.50 versus 0.83 and 0.51 versus 0.80). The study concluded that SF-36 is not specific enough to reflect the HRQoL issues of women with HMB.[97]

Overview of available evidence

No systematic reviews were identified on HRQoL 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 HRQoL as a primary outcome measure, and the baseline data may be used to show the impact of HMB.[101–107] Further detail is contained in evidence tables 3.4 and 3.5.

Quality of life of women with HMB

Three qualitative studies ($n = 200$; $n = 30$; $n = 43$) using interviews and focus groups reported the experience of women with HMB. These studies found 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.[108–110] [EL = 3; EL = 3; EL = 3]

Six studies showed an association between HMB and mental wellbeing.

Using a regression model, a cross-sectional study ($n = 865$) from the UK found that unemployment was a predictor of MBL > 80 ml.[111] [EL = 3]

In a second publication ($n = 952$), the study highlighted that the relationship between MBL and HRQoL was not a linear relationship, and that the impact on HRQoL was the same for women with MBL between 50 ml and 200 ml.[112] [EL = 3]

A study from the UK ($n = 840$) showed the impact HMB had on women and the reasons why women consulted for HMB. The study found 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, $P = 0.01$).[62] [EL = 2–]

One cross-sectional survey ($n = 2805$) from the USA found that HMB was associated with lower employment rates, with a mean of 3.6 weeks of labour lost per year and lost earnings of $1,692 per year. The study found that women with HMB rated their overall health lower than the general population (fair = 40 (10.7%) versus 149 (6.1%); poor = 16 (4.3%) versus 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 (95% CI 0.56 to 0.92).[113] [EL = 3]

A survey ($n = 200$) undertaken in Egypt showed that, in relation to gynaecological symptoms, menstrual disturbances and HMB were rated as the most important concerns of women.[114] [EL = 3]

An observational study (based on an RCT) ($n = 220$) from Finland found that the main impacts of HMB were physical and social issues, but not psychological. However, other studies have found that HMB was associated with worse psychological scores, although the causal pathway and direction were not established.[66] [EL = 2–]

One study ($n = 348$ and $n = 209$) found the following HRQoL problems among women with HMB: 'flooding' = 71.0%; clothes bloodstained = 58.9%; painful periods = 52.0%; cause of anxiety or depression = 50.3%; cause of moodiness or irritability = 68.4%; interfere with social life = 29.0%; interfere with hobbies = 34.2%; interfere with life in general = 43.4%.[115,116] [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.[117–119] [EL = 3; EL = 1+; EL = 1+]

3.4.2 Evidence statements on impact of HMB on quality of life

Evidence shows that HMB has a measurable effect on quality of life. There is evidence that HMB impacts on social interaction and, although 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.

Recommendations on impact of HMB on quality of life

Heavy menstrual bleeding (HMB) should be recognised as having a major impact on a woman's quality of life, and any intervention should aim to improve this rather than focusing on menstrual blood loss. [C]

Research recommendations on impact of HMB on quality of life

- The currently available HMB-specific HRQoL 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.

3.5 Prevalence of HMB

The section above highlights the impact that HMB has on the individual woman but does not address the effect on the wider population.

3.5.1 Review on prevalence of HMB

Overview of available evidence

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

Prevalence of HMB

The review reported prevalence of excessive menstrual bleeding of 4–9% from four studies. The review also reported on two World Health Organization (WHO) studies that identified HMB rates of 8–27% based on subjective assessment.[120] The WHO studies were undertaken in various locations around the world and thus the results may reflect sociocultural differences in how menstruation is perceived.

The primary studies reported rates of HMB of 11.0–51.6% but it is likely that differences in how menstruation is measured and in the populations sampled will account for some of the variation.[14,15,25–27,40,43,83,121,122]

Three studies objectively measured MBL.[25–27] The others used self-assessment methods.[14,15,40,121] Of the three studies that used objective measures, the first study ($n = 476$) found that 11% of women had an MBL greater than 80 ml.[25] [EL = 3] The second study ($n = 182$) reported that 13.5% of women had an MBL greater than 80 ml.[26] [EL = 3] The third study ($n = 348$) found that 26 (9%) of 280 women had an MBL greater than 80 ml.[27] [EL = 3]

Of the subjective studies, one study ($n = 1513$) reported prevalence of HMB of 51.6% and of 'increased' menstrual bleeding within the previous 6 months of 22.6%. At the 12 month follow-up, the study showed an incidence of HMB of 25.0% and for 'increased' menstrual bleeding of 20.5%.[41] [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%.[61] [EL = 3] A third cohort study ($n = 5292$) found that 19.5% of women reported heavy periods.[123] [EL = 3] A fourth study ($n = 3096$) found that 21% of women reported heavy periods.[124] [EL = 3] A fifth study ($n = 4610$) found that 30% of women reported having heavy periods.[122] [EL = 3]

3.5.2 Evidence statements on prevalence of HMB

Studies show that between 4% and 51.6% of women experience HMB. However, these results are based on figures from a number of different countries and clinical settings and the effects of these factors on the results have to be considered.

3.6 Definition of HMB

The sections above outline both the objective and subjective elements needed for defining HMB. There is evidence that women and clinicians find some of the definitions currently used for HMB unhelpful.[125,126] 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 has demonstrated that quality of life and MBL are not closely linked.[111,112] Another study has shown that the direct measurement of MBL in clinical settings is impractical.[126]

3.6.1 Evidence statements 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 definitions used in research studies, which are currently set at between 60 ml and 80 ml 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. Further detail is contained in evidence tables 3.1 to 3.5.

Recommendations on definition of HMB

For clinical purposes, HMB should be defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms. Any interventions should aim to improve quality of life measures. [D]

4 History taking, examination and investigations for HMB

Introduction

There are several frameworks for analysing the consultation between the doctor and the woman. One common approach is to recognise consultation styles as using a biological model where physical processes are measured and compared with a 'normal' reference. Another approach is 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 with which a woman presents.

Pathology in HMB may result as a consequence of the blood loss, it may cause the excessive blood loss, or it may 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. However, 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 may 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.

4.1 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.

4.1.1 Review on history taking for HMB

Overview of available evidence

No evidence was identified relating to history taking for women who present with HMB. This section is thus based on discussion within the GDG.

4.1.2 GDG discussion on history taking for HMB

The GDG identified three main areas of questioning.

Nature of bleeding

Initially the clinician should establish that the woman has menstrual bleeding that is, in her and the clinician's opinion, heavy.

While non-menstrual bleeding is outside the scope of this guideline, epidemiological evidence suggests that an alteration in the menstrual cycle, intermenstrual bleeding or post-coital bleeding may be the first symptoms of gynaecological cancer and indicate the need for a pelvic examination.[95] Persistent intermenstrual bleeding requires investigation to exclude malignancy.[95]

Symptoms suggesting possible significant pathology

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

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, the clinician should elicit details of what treatment the woman has already undergone, if any.

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

4.1.3 Evidence statements on history taking for HMB

Based on GDG discussion and results from the review of epidemiology of HMB (Chapter 3), history taking for HMB should cover three main objectives:

- to define the nature of bleeding
- to identify potential pathology
- to identify women's ideas, concerns, expectations and needs.

Recommendations on history taking for HMB

Initially, a history should be taken from the woman. This should cover the nature of the bleeding, related symptoms that might suggest structural or histological abnormality, impact on quality of life and other factors that may determine treatment options (such as presence of co-morbidity). [D(GPP)]

Clinicians should take into account the range and natural variability in menstrual cycles and blood loss when diagnosing HMB, and should discuss this variation with the woman. If the woman feels that she does not fall within the normal ranges, care options should be discussed. [D(GPP)]

If the history suggests HMB without structural or histological abnormality, pharmaceutical treatment can be started without carrying out a physical examination or other investigations at initial consultation in primary care, unless the treatment chosen is levonorgestrel-releasing intrauterine system (LNG-IUS). [D(GPP)]

If the history suggests HMB with structural or histological abnormality, with symptoms such as intermenstrual or post-coital bleeding, pelvic pain and/or pressure symptoms, a physical examination and/or other investigations (such as ultrasound) should be performed. [D(GPP)]

4.2 Measurement of menstrual blood loss

Measurement of MBL can be divided into three types:

- objective measurement of MBL via the collection of used sanitary material from the woman, from which blood content is estimated
- surrogate measurement of MBL using duration of menstruation or number of sanitary products used
- subjective assessment of MBL via the woman's estimated amount of menstrual material.

4.2.1 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.[127–132] [EL = III; EL = III; EL = II; EL = III; EL = II; EL = III] Three of these studies on the alkaline haematin method reported recovery rates between 95% and 105% of known blood totals.[127–129] [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 estimated that this can have a significant impact on the total.[133] [EL = II] Two small observational studies in secondary care found that formally measuring MBL and informing women as to whether they had normal or heavy menstruations did have an impact on future treatment decisions.[134,135] [EL = 2–; EL = II]

However, two qualitative studies ($n = 73$; $n = 20$) highlighted the impracticality of using direct material measures outside a research study.[125,126] 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.[126] [EL = 3] Another study showed that community medical practitioners found that medical definitions were unhelpful, there was a lack of standards of normality and there were difficulties in discussing menstruation, which resulted in individual practitioners making judgements in idiosyncratic ways.[125] [EL = 3]

Indirect measurement of MBL – pictorial blood loss assessment charts (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), which was first outlined in 1990.[136]

Six diagnostic and observational studies were identified examining the use of PBAC. Owing to the heterogeneity of the study populations, it was not possible to undertake a meta-analysis of these studies.[131,133,136–139]

The original study ($n = 18$; 55 cycles) undertaken in the UK investigated the use of PBAC compared with alkaline haematin, used a cut-off of ≥ 100 compared with an alkaline haematin cut-off of 80 ml, 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 equivalent to > 80 ml).[136] [EL = II]

A second study ($n = 288$) investigating the use of PBAC compared with alkaline haematin found 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.[131] [EL = II]

A third diagnostic study ($n = 103$) investigating the use of PBAC compared with alkaline haematin found that using a cut-off of 100 on PBAC gave a sensitivity of 97%, a specificity of 7.5%, a positive predictive value (PPV) of 62%, a negative predicative value (NPV) of 60% and a correlation coefficient of 0.466.[137] [EL = II]

A fourth study ($n = 56$) investigating the use of PBAC compared with alkaline haematin, using a regression analysis, found an association between PBAC scores and MBL ($P = 0.001$). At a PBAC score ≥ 100, sensitivity was 88%, specificity was 52% and false positives were 59%.[138] (EL = III)

A fifth study ($n = 307$) compared PBAC with alkaline haematin and found a sensitivity of 58% and a specificity of 75% at a PBAC score cut-off of 50.[139] [EL = III]

A sixth study ($n = 121$) compared PBAC with alkaline haematin and found a sensitivity of 86% and a specificity of 88% where PBAC ≥ 100 and MBL ≥ 80 ml. 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 > 80 ml. When extraneous blood loss estimation was included, 45 of 61 women had MBL > 80 ml.[133] [EL = II]

Table 4.1 provides a summary of the available evidence on PBAC. These results show a lack of consistency across the studies.

Table 4.1 Summary of evidence on the pictorial blood loss assessment chart (PBAC)

Reference	Number of participants	PBAC level for menorrhagia	Comparator measure	Sensitivity (%)	Specificity (%)
136	18	100	Alkaline haematin	86%	89%
131	288	100	Alkaline haematin	91%	81.9%
137	288	130	Alkaline haematin	97%	7.5%
138	53	185	Alkaline haematin	88%	52%
139	103	50	Alkaline haematin	58%	75%
133	53	100	Alkaline haematin	86%	88%

Surrogate and self-assessment measures of MBL

Eight observational studies were identified examining the use of surrogate or self-assessment of MBL.[42,46,111,123,131,140–142]

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 >80 ml, 28 of 59 periods (47%) termed heavy were ≤ 80 ml, and 32 of 57 (56%) termed medium were >80 ml).[140] [EL = II]

An observational study ($n=69$) found 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.[141] [EL = III]

An epidemiological study ($n=5292$) was conducted 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 ($n=420$): $r=0.35$ ($P<0.01$).[123] [EL = 3]

A study ($n=412$) found associations between pad use and MBL: $r=0.61$ ($P<0.005$) and between duration and MBL ($n=420$): $r=0.35$ ($P<0.01$).[42] [EL = III]

An observational study ($n=254$) found a relationship between duration of menses and MBL (periods lasting 3 days = 24.3 ml and periods lasting 6 days = 58.7 ml).[46] [EL = III]

A study ($n=952$) found in a regression model that clot size, ferritin level and frequency of pad change ($P=0.001$, $P=0.002$ and $P=0.006$, respectively) provide the best predictive model for MBL >80 ml.[111] [EL = 3]

A study ($n=288$) found that 66 (56%) women complaining of menorrhagia had MBL >80 ml, and 52 (44%) women complaining of menorrhagia had MBL < 80 ml. In comparison, 23 (13.5%) women who did not complain of menorrhagia had MBL >80 ml, and 147 (86.5%) women who did not complain of menorrhagia had MBL < 80 ml.[131] [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 ($P<0.001$).[142] [EL = III]

4.2.2 Evidence statements 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 not all material is always 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. Further details are provided in evidence tables 4.1 to 4.3.

4.2.3 GDG interpretation of 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.

Recommendations on measurement of menstrual blood loss

Measuring menstrual blood loss either directly (alkaline haematin) or indirectly ('pictorial blood loss assessment chart') is not routinely recommended for HMB. Whether menstrual blood loss is a problem should be determined not by measuring blood loss but by the woman herself. [D(GPP)]

Research recommendations on measurement of menstrual blood loss

- Investigate routine use of indirect measurements of menstrual blood loss in primary and secondary care.
- Need for quality of life research in HMB and menstruation.

4.3 Physical examination for HMB

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 the need for investigations.

4.3.1 Review on physical examination for HMB

Overview of available evidence

No evidence was identified relating to the physical examination of women who present with HMB. This section is thus based on discussion within the GDG.

4.3.2 Evidence statements on physical examination for HMB

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

4.3.3 GDG discussion on physical examination for HMB

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. The GDG highlighted that a general examination may be useful for identifying general medical conditions if suspected from history taking or observation.

Recommendations on physical examination for HMB

A physical examination should be carried out before all:

- LNG-IUS fittings*
- investigations for structural abnormalities
- investigations for histological abnormalities. [D(GPP)]

Women with fibroids that are palpable abdominally or who have intra-cavity fibroids and/or whose uterine length as measured at ultrasound or hysteroscopy is greater than 12 cm should be offered immediate referral to a specialist. [D(GPP)]

4.4 Laboratory tests for 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.

* See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

4.4.1 Review on laboratory tests for HMB

Hormone testing

Epidemiological studies have found no link between hormone levels and HMB.[143,144] [EL = 2–; EL = 3] No studies were found on hormone testing for menorrhagia.

Thyroid function test

One case–control study ($n = 428$) found 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%) had irregular cycles. Out of 214 normal controls, matched for age and weight, 196 (91.6%) had normal menstruation and 18 (8.4%) had irregular cycles.[52] [EL = 2+]

von Willebrand disease

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

One review identified five studies and found the prevalence of vWD to be between 5.3% and 20%.[145] [EL = 2–] A second review found a prevalence of 13% (95% CI 11.0% 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.[48] [EL = 2+]

One additional study ($n = 83$) found that 11 of 59 (19%) women with menorrhagia had a coagulation disorder. Five (45%) of 11 with coagulation disorders had life-threatening uterine blood loss. No subsequent studies were identified.[146] [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 80–95%.[145] [EL = 2–]

Full blood count

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

One epidemiological cohort study ($n = 24\,894$) undertaken in the USA found that the prevalence of iron deficiency among the general population of women of menstrual age is approximately 11% compared with only 1% for men, and concluded that one likely explanation for this difference is menstruation.[147] [EL = 3]

A second epidemiological study ($n = 748$) found that iron concentration decreased rapidly ($P < 0.01$) at > 80 ml MBL.[25] [EL = 3]

A third study ($n = 309$) found that all blood measures decreased with increased MBL. The figures showed how haemoglobin, serum iron and serum ferritin levels were changed by MBL: for < 20 ml ($n = 130$), they were 13.3 g/dl, 78.8 µg/dl and 28.5 ng/ml, respectively; for > 80 ml ($n = 10$), they were 12, 47.3 and 10.6, respectively.[148] [EL = 3]

A fourth study ($n = 313$) found that anaemia levels increased from 1.5% at an MBL of less than 20 ml to 10.3% for an MBL between 61 and 80 ml and to 50% for an MBL between 161 and 240 ml.[26] [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 (at MBL < 20 ml ($n = 48$) prevalence was 0%, at MBL of 60–80 ml ($n = 53$) prevalence was 17% and at MBL > 100 ml ($n = 46$) there was a prevalence of 26.1%).[149] [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 of 60–80 ml.

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 ng/ml. 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.[150] [EL = 2++]

4.4.2 Evidence statements on 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 5–20% in women complaining of HMB. Evidence from a review suggests that the 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 among those with objectively confirmed HMB (>80 ml), with prevalence being greater than 10% in this group. One review showed 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 for HMB

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

Recommendations on laboratory tests for HMB

A full blood count test should be carried out on all women with HMB. This should be done in parallel with any HMB treatment offered. [C]

Testing for coagulation disorders (for example, von Willebrand disease) should be considered in women who have had HMB since menarche and have personal or family history suggesting a coagulation disorder. [C]

A serum ferritin test should not routinely be carried out on women with HMB. [B]

Female hormone testing should not be carried out on women with HMB. [C]

Thyroid testing should only be carried out when other signs and symptoms of thyroid disease are present. [C]

4.5 Investigations for structural and histological abnormalities

Ultrasound scanning 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 obtain improved ultrasound images of the endometrium and endometrial cavity. These techniques can detect structural but not histological abnormalities.

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 that 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 of investigations for structural and histological abnormality

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 population specifically with HMB. The results thus have to be extrapolated for a population with HMB.

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 (TVS) (ten studies) the range of sensitivity was 48–100% and for specificity the range was 12–100%, for identification of any intrauterine pathology. For sonohysteroscopy (11 studies) the range of sensitivity was 85–100% and for specificity it was 50–100%, for identification of pathology. For hysteroscopy (three studies) the range of sensitivity was 90–97% and for specificity it was 62–93%. The review concluded that all three methods were at least moderately accurate at identifying uterine pathology.[151] [EL = 2++] The second review also showed a range of results for the various investigations.[152] [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 and thus ultrasound and hysteroscopy were examined as equals. The study found that ultrasound was successfully completed in 88% of cases compared with 77% for hysteroscopy. The study also found that ultrasound identified more uterine fibroids than hysteroscopy (94 versus 39) but fewer polyps (17 versus 37). The accuracy of ultrasound for identifying endometrial cancer was calculated: the sensitivity was 66.7%, specificity 55.7%, PPV 6.9% and NPV 97%. In terms of acceptability, 11% of the women found ultrasound 'unpleasant' compared with 27% and 29% for hysteroscopy and biopsy, respectively. The study concluded that ultrasound had both advantages and disadvantages over hysteroscopy.[69] [EL = Ib]

A prospective cohort study ($n = 223$) undertaken in Turkey compared TVS, hysteroscopy and saline infusion sonography, using biopsy and dilatation and curettage as reference methods. For TVS for identification of submucous fibroids compared with histology: sensitivity = 58.3% specificity = 94.8%, PPV = 46.7%, NPV = 96.7%, LR+ = 11.16, LR– = 0.44.[153] [EL = II]

Saline infusion sonography

The results from the first review on saline infusion sonography are presented above.[151] 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 saline infusion sonography was an accurate method for investigation of uterine pathology.[154] [EL = 2++]

A prospective cohort study ($n = 223$) undertaken in Turkey compared TVS, hysteroscopy and saline infusion sonography, using biopsy and dilatation and curettage as reference methods. For saline infusion sonography for identification of submucous fibroids compared with histology: sensitivity = 81.3%, specificity = 98.0%, PPV = 81.3%, NPV = 98.0%, LR+ = 40.35, LR– = 0.19.[153] [EL = II]

Hysteroscopy

Results from one systematic review have been reported above,[151] and results from a second systematic review and one subsequent RCT are reported in this section. The second review identified 65 primary papers on the use of hysteroscopy in endometrial disease. The review found 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%).[155] [EL = 2++]

A subsequent RCT ($n = 683$) on women with dysfunctional uterine bleeding (DUB) compared ultrasound with hysteroscopy (both with and without biopsy). The study found 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 versus 39), although hysteroscopy was better at identifying polyps (13 versus 37). The trial found that hysteroscopy had 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.[69] [EL = Ib]

A subsequent RCT ($n = 83$) on women referred for hysteroscopic assessment compared a rigid with a flexible hysteroscope. The study found that the flexible hysteroscope resulted in less pain and discomfort for the women during and after the procedure.[156] [EL = 1b]

A prospective cohort study ($n = 223$) undertaken in Turkey compared TVS, hysteroscopy and saline infusion sonography, using biopsy and dilatation and curettage as reference methods. For hysteroscopy for identification of submucous fibroids compared with histology: sensitivity = 90.9% specificity = 95.8%, PPV = 76.9%, NPV = 98.6%, LR+ = 21.67, LR− = 0.10.[153] [EL = II]

Additional information on imaging techniques can be found in evidence tables 4.5 and 4.6.[70,72,78,79,84,85,157–212,212–214]

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.[202] [EL = Ib]

Endometrial biopsy

A number of biopsy methods are available but the one most often tested in menstrual problems is the Pipelle® curettage tool.

One diagnostic RCT ($n = 683$) reported success rates for completion of biopsy of between 80% and 84% depending on method and patient population. The sensitivity, specificity, PPV and NPV 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%.[69] [EL = Ib]

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.[76] [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 NPV of biopsies for identifying adenomyosis were, respectively: 44.8%, 95.9%, 81.2% and 81.4%.[79] [EL = Ib]

A diagnostic study ($n = 269$) on women with AUB found that 154 of 170 (90.6%) samples obtained by Pipelle biopsy gave enough information for histology, compared with 66 of 97 (68%) of those obtained by dilatation and curettage ($P < 0.0001$ for difference).[215] [EL = II]

A diagnostic study ($n = 114$) examining the Pipelle biopsy found that in 62 (54.4%) cases adequate material for histology was retrieved.[216] [EL = III]

A diagnostic study ($n = 276$) on women with AUB compared biopsy with dilatation and curettage results and found that 220 (83%) of 265 of the biopsy and dilatation and curettage results were the same. Furthermore, in 44 cases (16%) biopsy provided more information, but in nine cases (3%) biopsy provided less information. [217] [EL = III]

A diagnostic study ($n = 37$) on women with AUB undertook biopsies of 37 women with known endometrial carcinoma and found that 25 (68%) of 37 biopsy samples were positive for endometrial cancer.[218] [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%) of cases, and Isaac was successful in 1194 (92%) of cases ($P < 0.001$).[219] [EL = III]

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.[69] [EL = Ib]

A diagnostic trial ($n = 411$) involving women with menorrhagia compared ultrasound and Pipelle with hysteroscopy alone and found that 14 benign lesions (18%) were missed by the combination ($P = 0.0076$), but two hyperplasia and one carcinoma were detected that were not found on hysteroscopy. Furthermore, ultrasound and biopsy was associated with less pain and higher acceptability than hysteroscopy.[220] [EL = 1b]

A diagnostic study ($n = 377$) found that combined hysteroscopy and biopsy made no difference to management options, compared with 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.[221] [EL = 1b]

A diagnostic study ($n = 78$) found that a combination of ultrasound and Pipelle biopsy may provide more robust assessment than using the investigations separately.[180] [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 of 68%, 78% and 81% where hysterectomy, dilatation and curettage or both were, respectively, used as the 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, dilatation and curettage or both were, respectively, used as reference method. The specificities were 100%, 99.1% and 100%, respectively.[222] [EL = II]

Health economics

No studies of MRI, ultrasound, saline infusion 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 infusion sonography or hysteroscopy. For a cohort of 1000 women 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 infusion sonography and 696 correct diagnoses at a cost of £209,720 using hysteroscopy.

4.5.2 Evidence statements 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 shows that ultrasound is an accurate method for identifying pathology (sensitivity 48–100% and specificity 12–100%). 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 infusion sonography is an accurate method for identification of pathology, with a sensitivity of 85–100% and a specificity of 50–100%. One review found that for hysteroscopy the sensitivity was 90–97%, and the specificity was 62–93%. 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 infusion sonography).

Eight studies found that biopsies had a successful completion rate of between 54% and 93%. The sensitivity of tests varied between 70% and 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 with hysteroscopy alone. No evidence was found on the population risk of endometrial cancer of women seen in secondary care for HMB. Further detail is provided in evidence tables 4.4 to 4.6.

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.

Based on clinical experience and the results of the systematic review, the GDG felt that saline infusion sonography should not be recommended as a first-line investigation.

The GDG recognised that particular investigative methods were better for identifying certain types of pathology than others. The GDG focused on the need to identify uterine fibroids, which are linked to HMB and to pre-malignant or malignant pathology, as identification of life-threatening pathology is essential.

Recommendations on investigations for HMB

If appropriate, a biopsy should be taken to exclude endometrial cancer or atypical hyperplasia. Indications for a biopsy include, for example, persistent intermenstrual bleeding, and in women aged 45 and over treatment failure or ineffective treatment. [D(GPP)]

Imaging should be undertaken in the following circumstances:

- the uterus is palpable abdominally
- vaginal examination reveals a pelvic mass of uncertain origin
- pharmaceutical treatment fails. [D(GPP)]

Ultrasound is the first-line diagnostic tool for identifying structural abnormalities. [A]

Hysteroscopy should be used as a diagnostic tool only when ultrasound results are inconclusive, for example, to determine the exact location of a fibroid or the exact nature of the abnormality. [A]

If imaging shows the presence of uterine fibroids then appropriate treatment should be planned based on size, number and location of the fibroids. [D(GPP)]

Saline infusion sonography should not be used as a first-line diagnostic tool. [A]

Magnetic resonance imaging (MRI) should not be used as a first-line diagnostic tool. [B]

Dilatation and curettage alone should not be used as a diagnostic tool. [B]

Where dilatation is required for non-hysteroscopic ablative procedures, hysteroscopy should be used immediately prior to the procedure to ensure correct placement of the device. [D(GPP)]

Research recommendations on investigations for HMB

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

5 Education and information provision

Introduction

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

- lead to more ethical decision making, as a woman with HMB can be enabled to play an active and informed role in decision making
- allow a 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 to 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.

5.1 Education and information provision for women with HMB

Patient education and information provision provide the cornerstones of modern health care. They are essential for patient empowerment, ethical and legal treatment provision, informed choice, informed consent and shared decision making.[223,224] A number of basic toolkits are available to help produce patient information and education resources.[225] The provision of 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.[226]

5.1.1 Review of information provision for women with HMB

Overview of available evidence

Nine observational or descriptive studies were identified that highlight the issues that are important to women with regard to the provision of information and the content of that information provision. Further detail is provided in evidence tables 5.1 to 5.4.

Information provision for women with HMB

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

- fear for sexual identity and relationship with partners before surgery
- freedom from pain and embarrassment
- improved sexuality and self-esteem after surgery.[227] [EL = 3]

A study ($n = 10$) using qualitative interviews examined the decision-making process that women go through before having a hysterectomy. The authors outlined a model containing four phases of decision making:

1. seeking solutions – finding information on symptoms that occur via friends and family, clinicians, etc.

2. hold on – changing lifestyle in order to cope with symptoms
3. changing course – single event usually triggering women to seek a solution to the problem
4. taking charge – is the time when the women organise and prepare for the hysterectomy.

This model is useful as it highlights where in the decision-making process women will need information.[228] [EL = 3]

A study ($n = 29$) used qualitative interviews to investigate women's experience of hysterectomy. The study found that most women delayed seeking formal medical help for as long as possible, often using complementary therapies. The study found that women often tried to get information about their condition as early as possible from various sources. Furthermore, the study found that women received a lot of information about hysterectomy from clinicians, but little information on alternatives. Women stated that they had a hysterectomy based on the advice of the gynaecologist, but that they were often told to think about the impact it would have and to delay the operation if they had serious social or psychological concerns with it. The study also highlighted that women were often still undecided after they agreed to surgery. Women also said that they were told to talk to family and friends about the procedure before making a decision.[228] [EL = 3]

A study ($n = 50$) used qualitative interviews to examine women's experience of hysterectomy. The main factors it identified were:

- a lack of information provision about the nature and the implications of hysterectomy
- most women were afraid of having major surgery
- women highlighted the need for support networks
- a lack of information during the recovery phase.[229] [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 and identified seven major themes:

1. positive aspects – 61 of the 102 women outlined positive aspects of treatment by hysterectomy, including relief from symptoms, accurate information, supportive physician and involvement in decision making
2. HRT – fears and concerns about using HRT, based on lack of information
3. insufficient information – 38 of 102 thought that 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 the 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.[230] [EL = 3]

A study ($n = 148$) from the USA used a survey to examine women's experience of hysterectomy and four main themes emerged:

1. The outcomes of hysterectomy: women identified the benefit of the relief from symptoms as a result of hysterectomy. Women also wanted minimally invasive surgery and quick recovery in order to return to work and family responsibilities. Women were concerned about the adverse effects of surgery, both physical and emotional.
2. The decision to have surgery: women consulted friends and family about the decision to have a hysterectomy, often using others' experience as a guide. Women wanted to have a clear rationale for having surgery from clinicians.
3. Women were also concerned about the loss of sexuality and the male response to hysterectomy.

4. Opinions on health care: women felt that clinicians were only interested in financial gain from doing a hysterectomy. Women wanted female doctors as they thought they were less likely to suggest a hysterectomy.

The survey results correlate with the findings of the qualitative studies, with women's concerns and fears about hysterectomy, and its psychosocial impacts, being highlighted.[231] [EL = 3]

A study ($n = 10$) that surveyed women's information requirements prior to hysterectomy outlined five elements that needed to be included:

1. advantages of hysterectomy
2. possible risks and adverse effects of hysterectomy
3. treatments available other than hysterectomy
4. advantages of treatments other than hysterectomy
5. disadvantages of treatments other than hysterectomy.

The study found that women felt that not enough information about the risks and disadvantages of surgery was provided prior to surgery. The study also highlighted that women sought information in addition to the information provided by clinicians, for a number of reasons. The information sought included: what hysterectomy involves, what effect hysterectomy has on the menstrual system, other effects of 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% and 30% of the women were neutral or dissatisfied. When asked questions about whether hysterectomy had been the right decision, approximately 10% of the women were neutral or disagreed.[232] [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. realign 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 other treatment options, improved quality of life, reduced distress, reduced regret, informed use of resources.[233] [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.[234] [EL = 3]

5.1.2 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 provision that is non-specific to HMB, and that has not been 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 this 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 with usual care, decision aids performed better in terms of:

- greater knowledge (WMD 18.75 out of 100 [95% CI 13.14 to 24.35])
- more realistic expectations (RR 1.4 [95% CI 1.1 to 1.9])
- lower decisional conflict related to feeling informed (WMD = –9.1 of 100 [95% CI –12 to –6])
- increased proportion of patients that controlled decision making (RR 1.49 [95% CI 0.99 to 2.25])
- reduced practitioner-controlled decision making (RR 0.68 [95% CI 0.53 to 0.89])
- reduced proportion of people who remained undecided post-intervention (RR 0.43 [95% CI 0.27 to 0.70]).

When simpler decision aids were compared with more detailed decision aids, the relative improvement was significantly better for the more detailed tools, for:

- knowledge (WMD 4 out of 100 [95% CI 3 to 6])
- more realistic expectations (RR 1.5 [95% CI 1.3 to 1.7])
- 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 means 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.[235] [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 examined 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 group OR 95% CI 1.46 to 4.20 and booklet and interview group 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 the SF-36 and EQ-5D scales. Furthermore, there was no difference between groups in terms of perceived involvement in treatment choice.[236] [EL = 1+]

A second RCT ($n = 569$) undertaken in Finland examined the use of an information booklet on HMB against no information or usual care. The study found that more women in the information group had a treatment preference after they had received the booklet than those in the control group (4% versus 11% had made no treatment decision by 3 months). However, there was no statistical difference between the groups in level of knowledge, satisfaction with clinic or anxiety. There were also no differences between groups on the SF-36 scores, visual analogue scale (VAS) perceived health, anxiety and psychosomatic symptoms, menstrual symptoms, sexuality and satisfaction with treatment, except for the emotional role on SF-36 ($P = 0.01$), where the intervention group improved more. However, scores for both intervention and control groups significantly improved from baseline to follow-up, except for sexuality scores. There were no statistically significant differences between the groups in terms of health service use or cost. The study concluded that the information booklet was of limited use.[237–239] [EL = 1–]

A third randomised study ($n = 40$) examined whether differences occurred when women were provided with standard information or specific risk of treatment information. The study found no

difference between groups for anxiety but significant differences for knowledge ($P = 0.002$) and satisfaction ($P < 0.001$) in favour of the specific information group.[240] [EL = 1–]

A fourth randomised study ($n = 60$) examined the use of a cognitive support method in women scheduled for hysterectomy. The study found that women in the cognitive group had fewer worries but less knowledge than the information group prior to surgery, and that both groups had less anxiety, fewer worries and better knowledge than the control group. The study found that, postoperatively, the cognitive group had fewer symptoms and fewer days of pain than the information group.[241] [EL = 1–]

A fifth randomised study ($n = 96$) examined cognitive training prior to surgery versus standard information provision. The study found that anxiety scores (60.17 (SD 6.56) versus 62.77 (SD 5.77), $P < 0.05$), pain scores (7.10 (SD 0.72) versus 7.35 (SD 0.56), $P < 0.05$) and patient satisfaction (47.38 (SD 3.89) versus 45.75 (SD 3.52), $P < 0.05$) all favoured the cognitive group. No difference in analgesic use was reported.[242] [EL = 1–]

Health economics

One economic evaluation ($n = 894$) met the criteria for inclusion and assessed 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 £1,333, interview plus information £1,030) and higher mean quality-adjusted life years (1.567 and 1.582, respectively) compared with the control group (£1,810, 1.574). The information plus interview intervention was dominant, having both the lowest mean cost and giving higher mean QALYs. Overall costs were 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) were excluded from the analysis, information plus interview remained the dominant intervention when compared with either the information alone or control groups. There was no difference in mean QALYs from the base-case analysis, and the mean costs for the interview group (£907) remained lower than for the control (£1,446) or the information only group (£995). In addition, when all inpatient and unrelated costs were excluded from the analysis, the information plus interview intervention remained dominant, with lower mean costs (£853) than either information alone (£946) or the control (£887). Again, there was no difference in the mean QALYs between this analysis and the base case.[236] [EL = 1+]

5.1.3 Evidence statements on education and information provision 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, owing to the heterogeneity of studies, was unable to show that decision aids improved patient outcome.

Three RCTs examined education provision for women and these found that education improved knowledge and women's ability 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. Further detail is provided in evidence tables 5.1 to 5.4.

5.1.4 GDG interpretation of evidence on education for women with HMB

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

The GDG discussion focused on the following:

- Clinicians should be aware that unwillingness (women may not want to express their thoughts and feelings to clinicians), inability (women may not know how to express their thoughts and feelings to clinicians) and ambivalence (women may have both positive and

negative feelings and be unable to express a clear opinion to clinicians) are all factors that can have an impact on 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 is the content of education 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.

Recommendations on education for women with HMB

A woman with HMB referred to specialist care should be given information before her outpatient appointment. The Institute's information for patients ('Understanding NICE guidance') is available from www.nice.org.uk/CG044publicinfo. [A]

Although respect for autonomy, and individual choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost-effective. [D(GPP)]

Women should be made aware of the impact on fertility that any planned surgery or uterine artery embolisation (UAE) may have, and if a potential treatment (hysterectomy or ablation) involves the loss of fertility then opportunities for discussion should be made available. [D(GPP)]

Women should be given the following information on potential unwanted outcomes.

Table 5.1 Potential unwanted outcomes of interventions for HMB

Intervention	**Potential unwanted outcomes experienced by some women** (common = 1 in 100 chance, less common = 1 in 1000 chance, rare = 1 in 10 000 chance, very rare = 1 in 100 000 chance)	
Levonorgestrel-releasing intrauterine system (LNG-IUS)	Common:	irregular bleeding that may last for over 6 months; hormone-related problems such as breast tenderness, acne or headaches, which, if present, are generally minor and transient
	Less common:	amenorrhoea
	Rare:	uterine perforation at the time of IUS insertion
Tranexamic acid	Less common:	indigestion; diarrhoea; headaches
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Common:	indigestion; diarrhoea
	Rare:	worsening of asthma in sensitive individuals; peptic ulcers with possible bleeding and peritonitis
Combined oral contraceptives (COCs)	Common:	mood changes; headaches; nausea; fluid retention; breast tenderness
	Rare:	deep vein thrombosis; stroke; heart attacks
Oral progestogen (norethisterone)	Common:	weight gain; bloating; breast tenderness; headaches; acne (but all are usually minor and transient)
	Rare:	depression

Table 5.1 (*cont.*)

Intervention	**Potential unwanted outcomes experienced by some women** (common = 1 in 100 chance, less common = 1 in 1000 chance, rare = 1 in 10 000 chance, very rare = 1 in 100 000 chance)	
Injected progestogen	Common:	weight gain; irregular bleeding; amenorrhoea; premenstrual-like syndrome (including bloating, fluid retention, breast tenderness)
	Less common:	small loss of bone mineral density, largely recovered when treatment is discontinued
Gonadotrophin-releasing hormone analogue (GnRH-a)	Common:	menopausal-like symptoms (such as hot flushes, increased sweating, vaginal dryness)
	Less common:	osteoporosis, particularly trabecular bone with longer than 6 months' use
Endometrial ablation	Common:	vaginal discharge; increased period pain or cramping (even if no further bleeding); need for additional surgery
	Less common:	infection
	Rare:	perforation (but very rare with second-generation techniques)
Uterine artery embolisation (UAE)	Common:	persistent vaginal discharge; post-embolisation syndrome – pain, nausea, vomiting and fever (not involving hospitalisation)
	Less common:	need for additional surgery; premature ovarian failure, particularly in women over 45 years old; haematoma
	Rare:	haemorrhage; non-target embolisation causing tissue necrosis; infection causing septicaemia
Myomectomy	Less common:	adhesions (which may lead to pain and/or impaired fertility); need for additional surgery; recurrence of fibroids; perforation (hysteroscopic route); infection
	Rare:	haemorrhage
Hysterectomy	Common:	infection
	Less common:	intra-operative haemorrhage; damage to other abdominal organs, such as the urinary tract or bowel; urinary dysfunction – frequent passing of urine and incontinence
	Rare:	thrombosis (DVT and clot on the lung)
	Very rare:	death
	(Complications are more likely when hysterectomy is performed in the presence of fibroids)	
Oophorectomy at the time of hysterectomy	Common:	menopausal-like symptoms

Implementation advice on improving education and information provision for women with HMB

This section provides advice on improving information provision, communication and education. The advice provided here is seen as fundamentally important to the successful provision of health care, and is seen a prerequisite for the implementation of the recommendations outlined in the rest of the guideline. The reason that these issues do not have recommendations is that they represent generic issues.

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

- Treatment decision making should involve negotiated agreement between the woman and the clinician.
- The woman should be allowed choice of treatment, but within the clinician's remit of balancing risks and benefits.
- The clinicians should elicit the woman's preferences and desired outcomes, help her to express concerns about treatment options and, as a result, devise an individualised treatment plan.
- Both the clinician and the woman should be aware that, when there is patient ambivalence and/or clinician uncertainty about optimal treatment, this may affect the shared decision-making process.
- The woman must have adequate time and support in the decision-making process, especially where the proposed treatment has irreversible results.
- The woman must be given the opportunity to review any treatment decision.
- The woman must have the option of obtaining a second medical opinion where a clinician has no knowledge or where opinions are at odds.
- The woman has the right to veto any treatment decision.
- Where a proposed treatment involves the loss of fertility, appropriate counselling and support should be made available to the woman.
- When no treatment is felt to be required then the woman must be reassured. This should involve a clear explanation for the decision and identifying why the woman has sought help, and then reassuring on these issues.
- Clinicians need training about maximising equality and equity of patient choice, and in how to provide emotional and psychological support as part of the consultation process.

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 of and recovery time from procedures
- likelihood of adverse events or complications occurring with a particular intervention
- likelihood that additional treatment will be required after a particular intervention
- absolute risks and benefits of the range of treatments
- list of healthcare providers offering relevant treatments for HMB
- potential wider social and psychological impacts of any treatment
- competencies required by clinicians for the relevant treatment options
- sources of further information and 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,[605] be 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?
6. Is it balanced and unbiased?

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

6 Choice

Introduction

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 patient's 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:

- the clinician imposes the treatment they feel is best on the patient (paternalistic decision making)
- the patient demands a treatment against the clinician's advice (consumerist decision making)
- the clinician and/or patient do 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.

6.1 Patient choice

6.1.1 Review on patient choice

Overview of available evidence

No review was scheduled for this question, as it was based purely on discussion among the GDG. However the GDG did use references to help their discussion.[239,243–255]

6.1.2 Evidence statement on patient choice

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

6.1.3 GDG discussion on patient choice

The *Social Value Judgements* document produced by NICE outlines the position of the organisation with regard to the provision of health care.[256] However, additional information and recommendations are provided here because of the importance of these issues in the management of HMB.

The recommendations made on patient choice were based on discussion within the GDG. No formal review of evidence was undertaken for this question, although 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 their having no clear preference or desire to make a choice, with the result that women often defer to the clinician's 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.[257] Clinician uncertainty or equipoise relates to their 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 women are making an irreversible decision, as counselling, information and education may help women to recognise their ambivalence and use it to make a 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 woman's understanding and expectations from any treatment, as these will affect satisfaction. If the clinician and woman can agree on an expected outcome then a management strategy can be developed to best achieve these results.
- The issues of equity and equality of access to care have to be considered in relation to patient choice. While 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 an informed decision.

Recommendations on choice for women with HMB

A woman with HMB should be given the opportunity to review and agree any treatment decision. She should have adequate time and support from healthcare professionals in the decision-making process. [D(GPP)]

A woman with HMB and/or her doctor should have the option of gaining a second medical opinion where agreement on treatment options for HMB is not reached. [D(GPP)]

7 Lifestyle interventions for HMB

Introduction

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.

7.1 Lifestyle interventions for HMB

7.1.1 Review on lifestyle interventions for HMB

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.

7.1.2 Evidence statement on lifestyle interventions for HMB

No evidence was identified.

8 Pharmaceutical treatments for HMB

8.1 Hormonal treatments for HMB

Heavy menstrual bleeding 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, such as increased fibrinolytic activity in the endometrium, increased prostaglandin levels or the presence of fibroids.

In women with HMB related to hormonal 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. 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 8.1 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.

Information from the individual RCTs included in the reviews can be found in evidence tables 8.1 to 8.9.[104,105,260–270] A summary of all pharmaceutical treatment options for HMB is given in Table 8.2 at the end of this chapter.

8.2 Intrauterine levonorgestrel-releasing systems (LNG-IUS)

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an intrauterine, long-term progestogen-only method of contraception licensed for 5 years of use. It has a T-shaped plastic frame with a rate-limiting membrane on the vertical stem that releases a daily dose of 20 micrograms of levonorgestrel. The effects of the LNG-IUS are local and hormonal, including prevention of endometrial proliferation and 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 LNG-IUS is also licensed for the management of idiopathic menorrhagia and as the progestogen component of an HRT regimen.

8.2.1 Review on LNG-IUS

Overview of available evidence

Two reviews[258,259] were identified. Further detail can be found in evidence tables 8.1 and 8.2.

LNG-IUS

A systematic review from 2005 identified ten RCTs comparing LNG-IUS with surgery or pharmaceutical treatments.[258] When comparing LNG-IUS against any pharmaceutical treatment (one RCT, $n = 35$), the review calculated the OR for amenorrhoea (>3 months) as 8.67 (95% CI 1.52 to 49.35) in favour of LNG-IUS. The OR for proportion unwilling to continue with treatment ($n = 91$) was 0.27 (95% CI 0.10 to 0.67) in favour of LNG-IUS. The OR for proportion of women satisfied with treatment (one RCT, $n = 40$) was 2.13 (95% CI 0.62 to 7.33).

When comparing LNG-IUS with endometrial ablation, the review calculated the OR for the proportion of women satisfied with treatment ($n = 136$) as 0.61 (95% 0.26 to 1.46). The OR for

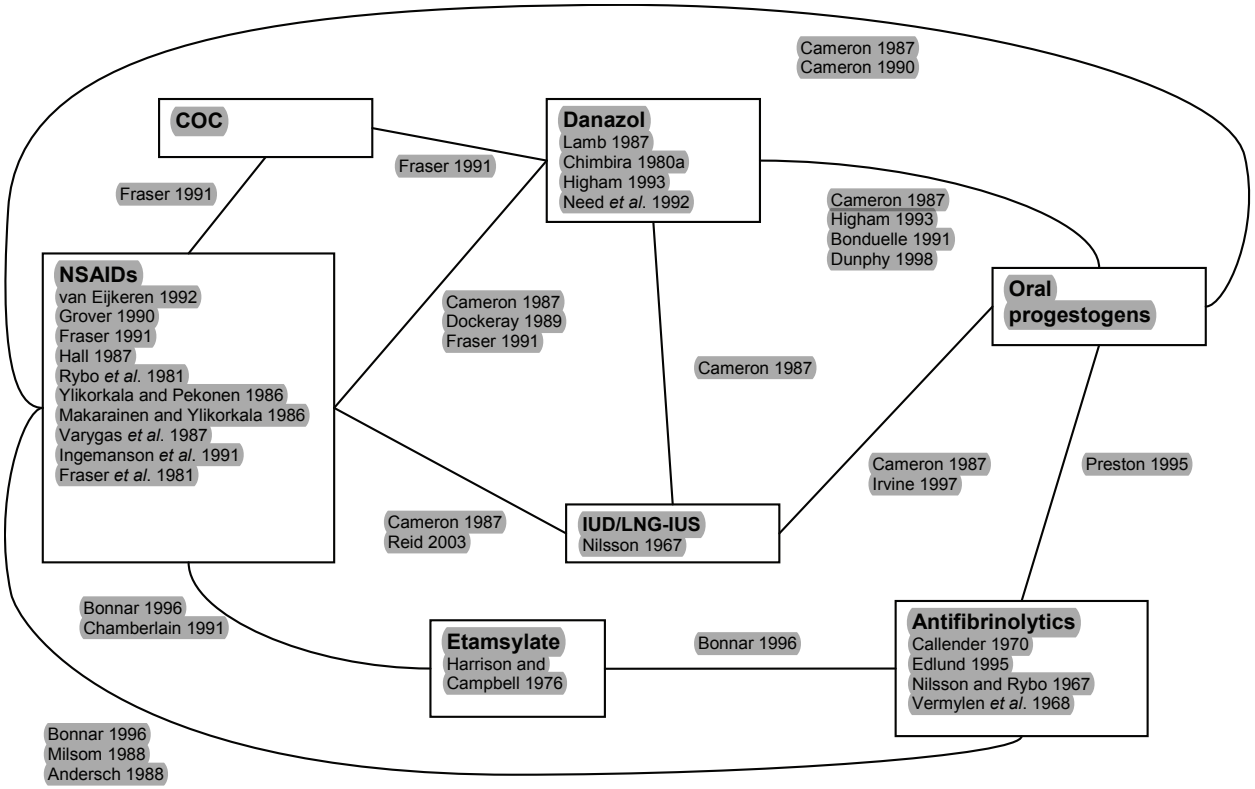


Figure 8.1 RCT evidence base for pharmaceutical interventions for HMB; trials comparing treatments are positioned along the line linking them; trials within the boxes are placebo controlled;[262,265,269,274,276–278,284,285,302,302–306,306,307,309,310,312–314,316–324] GnRH-a is not included here as it is an intervention for uterine fibroids rather than HMB and thus no comparative studies exist

amenorrhoea at up to 12 months ($n=223$) was 0.75 (95% CI 0.36 to 1.54) in favour of surgery. The WMD for PBAC score at 12 months (one RCT, $n=66$) was 33.2 ml (95% CI 27.2 ml to 39.2 ml) in favour of ablation.

When comparing LNG-IUS with hysterectomy, the study calculated the OR for satisfaction with treatment ($n=232$) as being 1.17 (95% CI 0.41 to 3.34) in favour of hysterectomy.[258] [EL = 1++]

In the second review ten studies met the inclusion criteria. This consisted of five RCTs and five case series. The review did not perform a meta-analysis but reported individual trial outcomes. The MBL reductions reported in the RCTs were between 71% and 96%.[259] [EL = 1+]

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 5 years when compared with hysterectomy. There was no statistically significant difference in quality of life scores at 5 years, as measured by the EQ-5D instrument, between the two treatment groups. Mean direct costs in the LNG-IUS arm remained significantly lower ($1,892) than the hysterectomy arm ($2,787), 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 pharmaceutical treatments (see Appendix A).[104]

No UK-based comparisons of LNG-IUS with any other medical or surgical treatment strategies were identified. In consultation with the GDG, a decision-analytic model was developed to examine the cost-effectiveness of pharmaceutical treatments as a first-line treatment for menorrhagia (for full results, see Appendix A). The results of the model showed that LNG-IUS generated more QALYs, at a lower cost, than any other pharmaceutical treatment strategy (Table 8.1).

Table 8.1 Summary of cost–utility analysis for pharmaceutical treatments at 5 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
COC pill	1,714,601	536,692	3610.71	−208.18	Dominated by LNG-IUS

COC = combined oral contraceptive; ICER = incremental cost-effectiveness ratio; LNG-IUS = levonorgestrel-releasing intrauterine system; NSAIDs = nonsteroidal anti-inflammatory drugs.

8.2.2 Evidence statements 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 96%. Evidence shows that the full benefit of treatment may not be seen for 6 months.

Economic modelling undertaken 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 combined oral contraceptive (COC) 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.

The GDG is aware that an RCT (ECLIPSE) is currently underway comparing LNG-IUS with other pharmaceutical treatments. These direct comparison data may prove useful for determining the place of LNG-IUS in the treatment of HMB.

Recommendations on LNG-IUS

The recommendations for LNG-IUS can be found at the end of this chapter.

8.3 Combined oral contraceptives

Combined oral contraceptives (COCs) contain estrogen 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.[271]

8.3.1 Review on COCs

Overview of available evidence

Two systematic reviews[272,273] and one primary study[274] were included in the review of COCs and HMB. Further detail is provided in evidence table 8.3.

COCs

Two systematic reviews were identified,[272,273] and these based their conclusions on the same RCT, which is described below.[274]

One RCT ($n = 45$) was identified on women with menorrhagia comparing COCs with naproxen, mefenamic acid and danazol. This comparative trial found that COCs reduced MBL by 43%, which was greater with than naproxen but less than with danazol or mefenamic acid. Adverse effects were not reported.[274] [EL = 1+]

Health economics

No heath economic studies were identified on the use of COCs for HMB. Decision-analytic modelling was undertaken for this guideline to assess the cost-effectiveness of certain pharmaceutical treatments as the first-line treatment for menorrhagia. This analysis showed than when compared with all other pharmaceutical treatment strategies, the COC pill generated fewer QALYs at a greater cost. When compared with a strategy of no treatment, the COC pill 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 was £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.

8.3.2 Evidence statements on COCs

Evidence from one RCT of COCs (ethinyl estradiol 30 micrograms and levonorgestrel 150 micrograms for 21 days) on short-term outcomes found a reduction of MBL of 43%. The study did not report adverse effects.

8.3.3 GDG interpretation of evidence on COCs

The GDG highlighted that there is no available data on 20 microgram COC preparations. The GDG also highlighted that the COC pill has other non-contraceptive benefits, such as cycle control, reduced breast pain and reduced dysmenorrhoea.

Recommendations on COCs

The recommendations for COCs can be found at the end of this chapter.

8.4 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 estrogen 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 adverse effect profiles. The mechanisms by which oral progestogens reduce MBL are not fully understood.

8.4.1 Review on oral progestogens

Overview of available evidence

Two systematic reviews were identified examining the use of progestogens during the luteal phase of the menstrual cycle. Further detail is provided in evidence table 8.4.

Oral progestogens used in the luteal phase only

The first review from 1995 (four RCTs) showed norethisterone had no effect on MBL (MBL percentage change: 95% CI −6.1% to +1.1%).[273] [EL = 1+]

The second review undertaken in 2003 (seven RCTs) showed that all other pharmaceuticals tested produced greater reductions in MBL than norethisterone (versus NSAIDs the change in MBL was −23.0 ml [95% CI −46.6 to 0.62] in favour of NSAIDs; versus danazol the change in MBL was −55.6 ml [95% CI −96.5 to −14.7] in favour of danazol; versus tranexamic acid the change in MBL was −111.0 ml [95% CI −178.5 to −43.5] in favour of tranexamic acid; and versus progesterone IUS the change in MBL was −51.0 ml [95% CI −83.6 to −18.4] in favour of IUS).[275] [EL = 1++]

Detailed information from the individual RCTs included in the above reviews can be found in the evidence table.[262,274,276–279]

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 104–107.5 ml prior to treatment to a range of 72–67 ml after treatment. However, this study only involved five women with menorrhagia and thus it is difficult to generalise the results.[280] [EL = 2−]

Oral progestogens throughout both the follicular and luteal phases

An RCT ($n = 44$) on women with menorrhagia examined the use of oral progestogens cyclically for 21 days compared with LNG-IUS. The trial found an 83% reduction associated with long-term use of oral progestogens compared with a 94% reduction with LNG-IUS; the difference between groups was not statistically significant. However, 22% of women were satisfied with oral progestogens compared with 66% with LNG-IUS (no statistics provided).[265] [EL = 1+]

Health economics

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

8.4.2 Evidence statements on oral progestogens

The evidence from two reviews shows that oral progestogens taken during the luteal phase of the menstrual cycle (for 7–10 days) have no effect on MBL. Evidence from one small trial shows that oral progestogen (norethisterone 15 mg daily from day 5 to day 26 of the cycle) used long-term reduces MBL by 83%.

8.4.3 GDG interpretation of evidence on oral progestogens

The GDG discussion highlighted that:

- other oral progestogens may be equally effective, but supportive data are not available
- progestogen use for heavy menstrual loss requires a long-course regimen
- while progestogens are effective, their clinical usefulness may be limited by tolerability.

Recommendations on oral progestogens

The recommendations for oral progestogens can be found at the end of this chapter.

8.5 Other hormonal treatments for HMB

Danazol is a synthetic androgenic steroid with anti-estrogenic 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 adverse effects similar to those of danazol but is only required to be taken twice weekly as opposed to daily.

8.5.1 Review on other hormonal treatments for HMB

Overview of available evidence

Two systematic reviews[273,281] and one primary study[282] were identified. Further detail is provided in evidence table 8.5.

Other hormonal treatments

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%).[273] [EL = 1+]

A second review included nine RCTs and found that danazol reduced MBL more than NSAIDs (one study; WMD −96.7 ml [95% CI −138.8 to −54.6]) or progestogens (one study; WMD −35.6 ml [95% CI −102.2 ml to +31 ml), but it also caused more adverse effects than NSAIDs (OR 7.0 [95% CI 1.7 to 28.2]) or progestogens (OR 4.05 [95% CI 1.6 to 10.2]).[281] [EL = 1++]

Information from the individual RCTs included in the systematic reviews can be found in the evidence tables.[262,276,277,283–285]

One small non-randomised trial ($n = 37$) compared gestrinone with a placebo. The study found that MBL was reduced in 15 of 19 women during the gestrinone treatment phase ($P < 0.01$) and that there was no change in MBL during placebo treatment. Adverse effects included dizziness, headaches, giddiness and tiredness in both groups.[282] [EL = 2++]

Health economics

No heath economic studies were identified on the use of danazol for HMB.

8.5.2 Evidence statements on other hormonal treatments for HMB

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

8.5.3 GDG interpretation of evidence on other hormonal treatments for HMB

In their interpretation of the evidence for pharmaceutical treatments, the GDG placed a high value on reduction of MBL and minimising adverse effects. Based on these criteria, the risk–benefit analysis for danazol was balanced against recommending its use.

Recommendations on other hormonal treatments for HMB

The recommendations for other hormonal treatments can be found at the end of this chapter.

8.6 Injected/depot progestogens

Medroxyprogesterone acetate (Depo-Provera®; Pharmacia) can be injected intramuscularly to provide contraception for the following 12 weeks. A subdermal etonogestrel implant is also available, which achieves lower serum concentrations by using diffusion technology and is licensed as a contraceptive for 3 years. These preparations currently have no licence for the treatment of HMB.

8.6.1 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 are data for the impact on MBL, specifically amenorrhea rates, when used as a contraceptive (this is taken from the NICE *Long-acting Reversible Contraception* guideline).[286]

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).[287] [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 9–10% of women in the first 3 months and by 41–47% of women at 1 year.[288] [EL = 1–]

In a study that assessed the effect of counselling on adherence in DMPA users, amenorrhoea was the major side effect reported, occurring in 34–35% of the women.[289] [EL = 3]

Health economics

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

8.6.2 Evidence statements on injected progestogens for HMB

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 contraception highlights that amenorrhoea is a side effect of injected progestogens.

Amenorrhoea is likely to occur during use of injectable contraceptives.

Recommendations on injected progestogens for HMB

The recommendations for injected progestogens can be found at the end of this chapter.

8.7 Hormone replacement therapy (HRT)

Estrogen 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 estrogen. Hormone replacement therapy (HRT) is not licensed for the treatment of HMB and may not contain a high enough dose of estrogen or progestogen to control an irregular cycle.

8.7.1 Review on HRT for treating HMB

Overview of available evidence

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

Health economics

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

8.7.2 Evidence statements on HRT for treating HMB

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 HMB.

8.7.3 GDG interpretation of evidence on HRT for treating HMB

The GDG highlighted that HRT will theoretically redress the imbalance that results from anovulatory cycles, but to achieve this HRT with a higher dosage of progestogen may be required.

Recommendations on HRT for treating HMB

The recommendations for HRT can be found at the end of this chapter.

8.8 Gonadotrophin-releasing hormone analogue for treatment of HMB associated with uterine fibroids

A gonadotrophin-releasing hormone (GnRH) agonist is a synthetic peptide that acts like the natural GnRH secreted by the hypothalamus but which has a much longer biological half-life. As a result, there is an initial increase in follicle-stimulating hormone (FSH) and luteinising hormone (LH) secretion (the so-called flare effect). However, after about 10 days a profound hypogonadal effect is achieved through downregulation. Generally, this induced and reversible hypogonadism is the therapeutic goal. With no production of FSH or LH, there is no follicular development and estrogen production, no ovulation, no progesterone production and no menses. GnRH agonists (GnRH-a) are thus useful in the treatment of cancers that are hormonally sensitive, such as prostate cancer and breast cancer. GnRH agonists are also useful in the pharmaceutical treatment of estrogen-dependent lesions such as endometriosis and uterine leiomyoma. Current agonists used are given by subcutaneous or intramuscular injection or intranasally.

8.8.1 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 they did also report data on the effect on MBL. Further detail is provided in evidence table 8.6.

GnRH-a

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

outcomes on menorrhagia compared with placebo (leuprolide acetate group ($n=38$): menorrhagia resolved or improved in 37 women, and no change or worse in one; placebo group ($n=37$): menorrhagia resolved or improved in 26 women, and no change or worse in 11). However, all reported adverse effects were significantly higher in the leuprolide acetate group compared with placebo (hot flushes: leuprolide acetate 52 (83%) versus placebo 5 (8%) ($P<0.0001$); vaginitis: 11 versus 0 ($P<0.0005$); arthralgia: 9 versus 0 ($P<0.005$); asthenia: 10 versus 3 ($P<0.05$); peripheral oedema: 7 versus 1 ($P<0.05$); insomnia: 6 versus 0 ($P<0.05$); nausea: 6 versus 1 ($P<0.05$); headaches: 18 versus 13; depression: 7 versus 2; emotional stability: 5 versus 1; decreased libido: 2 versus 0). The study concluded that treatment reduces MBL compared with 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 [95% CI 1.12 to 1.72]).[290] [EL=1+]

An RCT ($n=67$) on women with symptomatic uterine fibroids compared buserelin MP 1.8 mg with depot leuprorelin 1.88 mg 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; leuprorelin: 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 leuprorelin was associated with more hot flushes than buserelin (hot flushes at 12 weeks: buserelin=5.9%, leuprorelin=24.4%). The study shows that depot GnRH-a reduces menstrual bleeding. However, the study had high drop-out rates (11 of the buserelin and 15 of the leuprorelin group were lost to follow-up by 24 weeks).[291] [EL=1–]

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

Some types of HRT are licensed for use as 'add-back' therapy. It is used in combination with GnRH-a to overcome hormone-related adverse effects associated with GnRH-a.

Overview of available evidence

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

GnRH-a with HRT 'add-back'

A crossover RCT ($n=16$) on women with symptomatic uterine fibroids compared GnRH-a alone with GnRH-a plus medroxyprogesterone acetate (MPA) over 24 weeks. The study found that total uterine volume decreased to 73% of the baseline at 12 weeks in protocol B (monotherapy) ($P<0.04$), 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 crossover, MPA addition was associated with a significant increase in total uterine volume (protocol B) compared with a decrease in protocol A at 24 weeks ($P<0.005$). The study found that delayed use of 'add-back' allowed GnRH-a to shrink uterine fibroids. However, the study was small and the results can thus not be generalised. Furthermore, the study did not assess MBL outcomes.[292] [EL=1+]

An RCT ($n=16$) on women with symptomatic uterine fibroids compared leuprolide acetate only with leuprolide acetate plus MPA over a 24 week period. Women in group A (monotherapy) had a significant reduction in uterine size from a pre-treatment volume of 601 ± 62 cm^3 (mean ± standard error) to a mean uterine volume of 294 ± 46 cm^3 at 24 weeks of therapy ($P<0.01$). Women in group B (combined therapy) had a reduction in uterine volume, from 811 ± 174 cm^3 to 688 ± 154 cm^3, which was not statistically significant. However, only one woman in group B experienced hot flushes, whereas six women in group A had this symptom ($P<0.01$). This study suggests that simultaneous use of GnRH-a and 'add-back' reduces the effect of GnRH-a. However, the study was small and the results can thus not be generalised.[293] [EL= 1–]

An RCT ($n=51$) on women with symptomatic uterine fibroids compared GnRH-a plus estrogen-progestin 'add-back' with GnRH-a plus progestin 'add-back'. The study found that the symptoms of both groups improved (18 of 18 women in the estrogen-progestin group improved and 14 of 17 women in the progestin group improved), and that reduction in bone mineral density was similar in both groups (estrogen-progestin: pre-treatment=1.102 g/cm^3, 12 weeks=1.074 g/cm^3, 52 weeks=1.053 g/cm^3 ($P< 0.05$); progestin: pre-treatment=1.081 g/cm^3, 12 weeks=1.045 g/cm^3,

52 weeks = 1.047 g/cm³ ($P < 0.05$); control: pre-treatment = 1.081 g/cm³, 52 weeks = 1.078 g/cm³ (non-significant)). The study concluded that the regimens 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 women) was of concern.[294] [EL = 1–]

An RCT ($n = 12$) on women with symptomatic uterine fibroids compared GnRH-a with GnRH-a plus estriol 'add-back' over 6 months. The study found a reduction in mean fibroid size of 53.6% by 2 months and a further 31.3% by 6 months in the non-'add-back' group, and in the 'add-back' group a reduction in mean fibroid size of 59.1% by 2 months and a marginal further reduction by 6 months. Bone mineral density reduced to 96.5% of its original density by 2 months and to 92.5% by 6 months in the non-'add-back' group, but did not change significantly in the 'add-back' group. The study concluded that GnRH-a plus estriol 'add-back' therapy might be considered for long-term treatment of uterine leiomyomas. However, the study was small and the results can thus not be generalised.[295] [EL = 1–]

An RCT ($n = 50$) on women with symptomatic uterine fibroids compared GnRH-a plus placebo with GnRH-a plus tibolone over a 6 month period. The study found that menorrhagia improved in both groups (mean menorrhagia scores (0 to 10): baseline 8.2 versus 8.0, 6 months 0 versus 2.5 (both $P < 0.01$ from baseline)), but bone mineral density was reduced least in the tibolone group (baseline 1.056 g/cm³ versus 1.044 g/cm³, 6 months 1.002 g/cm³ versus 1.035 g/cm³ ($P < 0.01$ for placebo group versus baseline and versus treatment)). The study concluded that administering tibolone in association with GnRH-a reduces vasomotor symptoms and prevents bone loss, without compromising the therapeutic efficacy of GnRH-a alone.[296] [EL = 1–]

An RCT ($n = 100$) on women with symptomatic uterine fibroids compared GnRH-a plus raloxifene with GnRH-a plus placebo. The study found that bone mineral density levels fell significantly in the placebo group in comparison with the baseline and in comparison with the treatment group ($P < 0.05$). The study concluded that raloxifene prevents GnRH-a related bone loss in premenopausal women with uterine leiomyomas. The study did not assess MBL outcomes.[297] [EL = 1–]

Further results from this RCT examined the HRQoL impact of treatment compared with placebo and compared with healthy controls (GnRH-a plus raloxifene ($n = 45$) versus GnRH-a plus placebo ($n = 46$) versus normal population ($n = 50$)). The study found that cognitive functioning was adversely affected by treatment but that HRQoL was improved (Kupperman index (0 to 51): baseline = 2.6 (SD 1.2) versus 2.1 (SD 1.1) versus 2.1 (SD 1.2), sixth cycle = 22.8 (SD 3.9) versus 25.6 (SD 4.2) versus 2.5 (SD 1.3); SF-36: baseline = 50.4 (SD 14.1) versus 52.6 (SD 14.5) versus 84.2 (SD 10.4); sixth cycle = 80.3 (SD 11.5) versus 81.7 (SD 12.6) versus 83.4 (SD 10.2)). The paper concluded that GnRH-a causes a reduction in cognitive functioning in women with symptomatic fibroids but improves HRQoL to near-normal levels.[298]

An RCT ($n = 12$) on women with symptomatic uterine fibroids compared GnRH-a with 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 (treatment versus placebo: uterine volume at baseline = 645 cm³ versus 457 cm³ (non-significant), post-treatment uterine volume = 467 cm³ versus 656 cm³ ($P < 0.02$); myoma volume at baseline = 402 cm³ versus 267 cm³, post-treatment myoma volume = 334 cm³ versus 417 cm³ ($P = 0.06$)). 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 the results can thus not be generalised.[299] [EL = 1–]

Health economics

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

8.8.3 Evidence statements on GnRH-a

Evidence from two trials shows that GnRH-a reduces MBL, in the form of amenorrhea, with an RR of 1.39 [95% CI 1.12 to 1.72] for improvement in MBL, and amenorrhea rates of 89%.

However, GnRH-a is associated with significant adverse effects, including perimenopausal symptoms, headaches and nausea.

Evidence from seven RCTs shows that GnRH-a causes fibroid shrinkage and a decrease in MBL. However, the effects do not continue after stopping treatment and adverse effects preclude long-term use. The addition of 'add-back' therapy should not alter efficacy and prevents the majority of the adverse effects.

Recommendations on GnRH-a

The recommendations for GnRH-a can be found at the end of this chapter.

8.9 Non-hormonal pharmaceutical 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 the endometrium. 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.

A summary of all pharmaceutical treatment options for HMB is given in Table 8.2 at the end of this chapter.

8.10 Tranexamic acid

Tranexamic acid is a competitive inhibitor of plasminogen activation, thus acting as an antifibrinolytic agent. 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 with those not taking the drug when large communities are studied.

Tranexamic acid does not appear to affect platelet numbers or aggregation but acts to reduce the breakdown of fibrin in a pre-formed 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 1 g (2 × 500 mg tablets) three to four times daily, from the onset of bleeding for up to 4 days.

8.10.1 Review on tranexamic acid for treating HMB

Overview of available evidence

This review includes three systematic reviews. No additional or subsequent primary studies were identified relating to those studies included in the systematic reviews. Further detail is provided in evidence table 8.7.

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.[273,300,301] 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 seven trials and found a reduction in MBL of 46.7% (95% CI 47.9% to 51.6%) with tranexamic acid.[273] [EL = 1+]

The second review undertook a meta-analysis of two RCTs of tranexamic acid versus placebo and found a difference of −93.96 ml (95% CI −151.43 ml to −36.49 ml), $P = 0.001$, in favour of treatment.[300] [EL = 1++]

* IUD here refers to copper products, not LNG-IUS.

A third review based on five trials concluded that oral tranexamic acid 2.0–4.5 g daily for 4–7 days per cycle reduced MBL by 34–59% over two to three cycles, and that 12% of women reported adverse events, such as nausea, vomiting, diarrhoea and dyspepsia.[301] [EL = 1+]

There were no reports of deep vein thrombosis in any study in any of the reviews.[299–301]

Additional data from individual RCTs is available in evidence table 8.7.[279,302–307]

Health economics

No health economic studies were identified on the use of tranexamic acid to treat HMB. Decision-analytic modelling was undertaken for this guideline to assess the cost-effectiveness of certain pharmaceutical 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.

8.10.2 Evidence statements on tranexamic acid for treating HMB

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 2.0–4.5 g 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 1 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 QALY when comparing tranexamic acid with no treatment is £1,122.

8.10.3 GDG interpretation of evidence on tranexamic acid for treating HMB

The GDG highlighted that tranexamic acid:

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

Recommendations on tranexamic acid for treating HMB

The recommendations for tranexamic acid can be found at the end of this chapter.

8.11 Nonsteroidal anti-inflammatory drugs (NSAIDs)

A variety of NSAIDs have been used to treat HMB. These agents reduce prostaglandin synthesis by inhibition of cyclooxygenase. 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. When NSAIDs are taken to reduce HMB, they should be taken regularly from the onset of bleeding, or just before, until heavy loss has abated.

8.11.1 Review on NSAIDs for treating HMB

Overview of available evidence

Two systematic reviews met the inclusion criteria. No additional or subsequent primary studies were identified relating to those studies included in the systematic reviews. Further detail is provided in evidence table 8.8.

NSAIDs

One systematic review undertook meta-analysis on individual NSAIDs and found a range of responses, the highest being for mefenamic acid and the lowest for ibuprofen (mefenamic acid (pooled results for ten studies) reduction in MBL = 29.0% [95% CI 27.9% to 30.2%]; diclofenac (two studies) reduction in MBL = 26.9% [95% CI 23.3% to 30.6%]; naproxen (five studies) reduction in MBL = 26.4% [95% CI 24.6% to 28.3%]; ibuprofen (three studies) reduction in MBL = 16.2% [95% CI 13.6% to 18.7%]).[273] [EL = 1++]

A second review included only one placebo-controlled study but several comparative studies. The analysis showed that NSAIDs reduced MBL, but that tranexamic acid and danazol produced greater reductions (difference in reduction of MBL: NSAIDs versus placebo (one study, $n = 11$) −124 ml [95% CI −186 to −62]; NSAIDs versus tranexamic acid (one study, $n = 48$) +73 ml [95% CI 22 to 124]; NSAIDs versus etamsylate (two studies, $n = 82$) −43 ml [95% CI −86 to +0.5]; NSAIDS versus danazol (three studies, $n = 79$) +45 ml [95% CI 19 to 71]; NSAIDs versus oral progestogens (two studies, $n = 48$) −23 ml [95% CI −47 to +0.6]; NSAIDs versus IUD (one study, $n = 16$) −4 ml [95% CI −31 to +23]; NSAIDs versus oral contraceptive (one study, $n = 26$) +25 ml [95% CI −22 to +73]). However, NSAIDs had a better adverse effect profile than danazol, and a similar one to that of tranexamic acid.[308] [EL = 1++]

Further information on individual RCTs can be found in the evidence table.[262,274,284,305,306,309–318]

Health economics

No health economic studies were identified on the use of NSAIDs to treat HMB. Decision-analytic modelling was undertaken for this guideline to assess the cost-effectiveness of certain pharmaceutical 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.

8.11.2 Evidence statements on NSAIDs for treating HMB

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 adverse effect profile than 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.

8.11.3 GDG interpretation of evidence on NSAIDs for treating HMB

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
- owing to the cyclical nature of use, well-known adverse effects associated with long-term use of NSAIDs are reduced
- there is no evidence regarding the effect of NSAIDs on HMB in the presence of uterine fibroids, as women with fibroids were excluded from the trials
- NSAIDs should not be used where it is thought that HMB is caused by coagulation bleeding disorders.

Recommendations on NSAIDs for treating HMB

The recommendations for NSAIDs can be found at the end of this chapter.

8.12 Etamsylate

Etamsylate is believed to reduce bleeding from capillaries by correcting anomalies of platelet adhesion. It does not appear to affect the fibrin cascade. It is taken as 500 mg four times daily from, but not before, the onset of bleeding.

8.12.1 Review on etamsylate for treating HMB

Overview of available evidence

Three systematic reviews were identified that assessed the use of etamsylate.[273,300,308] No additional or subsequent primary studies were identified with regard to those studies included in the systematic reviews. Further detail is provided in evidence table 8.9.

One review pooled results of four studies and found etamsylate reduced MBL in HMB by 13.1% (95% CI 10.9% to 15.3%), but this was less than most other interventions.[273] [EL = 1+]

A review compared etamsylate with NSAIDs and found NSAIDs were more effective at reducing MBL (reduction in MBL for NSAIDs versus etamsylate = 43 ml [95% CI −0.5 to 86]).[308] [EL = 1++]

A review compared antifibrinolytics with etamsylate and found the former reduced MBL more than the latter (reduction in MBL for antifibrinolytics versus etamsylate (one study) = 97 ml [95% CI 60 to 134] in favour of tranexamic acid).[300] [EL = 1++]

Information on individual RCTs included in the reviews can be found in the evidence table.[305,310,319]

Health economics

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

8.12.2 Evidence statements on etamsylate for treating HMB

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.

Recommendations on etamsylate for treating HMB

The recommendations for etamsylate can be found at the end of this chapter.

GDG interpretation of evidence on pharmaceutical treatments for HMB

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 based their assessment firstly on the clinical effectiveness of treatments and secondly on the cost-effectiveness of treatments. The results of the systematic review showed that LNG-IUS, NSAIDs, tranexamic acid and COCs could be considered equivalent in terms of effectiveness. Health economic modelling showed that the LNG-IUS was the preferred treatment option when long-term use of a treatment was required. Further details can be found in evidence tables 8.1 to 8.9.

Recommendations on pharmaceutical treatments for HMB

Pharmaceutical treatment should be considered where no structural or histological abnormality is present, or for fibroids less than 3 cm in diameter which are causing no distortion of the uterine cavity. [D(GPP)]

The healthcare professional should determine whether hormonal contraception is acceptable to the woman before recommending treatment (for example, she may wish to conceive). [D(GPP)]

If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or non-hormonal treatments are acceptable, treatments should be considered in the following order:*

1. levonorgestrel-releasing intrauterine system (LNG-IUS) provided long-term (at least 12 months) use is anticipated†‡ [A]
2. tranexamic acid [A] or nonsteroidal anti-inflammatory drugs (NSAIDs) [A] or combined oral contraceptives (COCs) [B]
3. norethisterone (15 mg) daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestogens.§ [A]

If hormonal treatments are not acceptable to the woman, then either tranexamic acid or NSAIDs can be used. [D(GPP)]

Women offered an LNG-IUS should be advised of anticipated changes in the bleeding pattern, particularly in the first few cycles and maybe lasting longer than 6 months. They should therefore be advised to persevere for at least 6 cycles to see the benefits of the treatment.¶ [D(GPP)]

If pharmaceutical treatment is required while investigations and definitive treatment are being organised, either tranexamic acid or NSAIDs should be used. [D(GPP)]

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

Ongoing use of NSAIDs and/or tranexamic acid is recommended for as long as they are found to be beneficial by the woman. [D(GPP)]

Use of NSAIDs and/or tranexamic acid should be stopped if it does not improve symptoms within three menstrual cycles. [D(GPP)]

When a first pharmaceutical treatment has proved ineffective, a second pharmaceutical treatment can be considered rather than immediate referral to surgery. [D]

Use of a gonadotrophin-releasing hormone analogue could be considered prior to surgery or when all other treatment options for uterine fibroids, including surgery or uterine artery embolisation (UAE), are contraindicated. If this treatment to be used for more than 6 months or if adverse effects are experienced then hormone replacement therapy (HRT) 'add-back' therapy is recommended.** [B]

Danazol should not be routinely used for the treatment of HMB. [A]

Oral progestogens given during the luteal phase only should not be used for the treatment of HMB. [A]

Etamsylate should not be used for the treatment of HMB. [A]

Research recommendations on pharmaceutical treatments for HMB

- A study to investigate the use of LNG-IUS in fibroids greater than 3 cm.
- A study to examine the association between size and site of uterine fibroids and HMB.

* World Health Organization 'Pharmaceutical eligibility criteria for contraceptive use' (WHOMEC) apply. These criteria can be used to assess the individual's suitability for particular contraceptives. This allows informed decision making by the woman prior to the start of treatment. [www.ffprhc.org.uk/admin/uploads/298_UKMEC_200506.pdf]

† Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

‡ See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

§ Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented within the notes. In adolescents and women older than 40 years, refer to CSM advice issued in November 2004. Go to www.mhra.gov.uk and search for Depo Provera.

¶ See 'Long-acting reversible contraception', NICE clinical guideline 30, www.nice.org.uk/CG030, for more detail.

** Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

Table 8.2 Pharmaceutical options for treating HMB; discuss the risks and benefits of each option with the woman and provide information and support to aid decision making

Pharmaceutical treatment	How it works	What is it?	Effect on menstrual bleeding	Is it a contraceptive?	Will it impact on future fertility?	Possible unwanted outcomes
Levonorgestrel-releasing intra-uterine system (LNG-IUS)	Prevents proliferation of the endometrium	A small plastic device, placed in the uterus, which slowly releases progestogen	Bleeding reduced by up to 95%; full benefit may not be seen for 6 months	Yes	No	Common: irregular bleeding that may last for over 6 months; hormone-related problems such as breast tenderness, acne or headaches, which, if present, are generally minor and transient Less common amenorrhoea Rare: uterine perforation at the time of IUS insertion
Tranexamic acid	It is an antifibrinolytic	Two tablets orally, 3 to 4 times a day, from day 1 of the cycle for up to 4 days	Bleeding reduced by up to 58%	No	No	Less common: indigestion; diarrhoea; headaches
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Reduces production of prostaglandin	Tablets orally from day 1, or just before, until heavy blood loss has stopped	Bleeding reduced by up to 49%	No	No	Common: indigestion; diarrhoea Rare: worsening of asthma in sensitive individuals; peptic ulcers with possible bleeding and peritonitis
Combined oral contraceptives (COCs	Prevents proliferation of the endometrium	One pill daily for 21 days, followed by a 7 day break	Bleeding reduced by 43%	Yes	No	Common: mood changes; headaches; nausea; fluid retention; breast tenderness Rare: deep vein thrombosis; stroke; heart attacks
Oral progestogen (norethisterone)	Prevents proliferation of the endometrium	Tablets, orally, 15 mg from day 5 to day 26 of cycle	Bleeding reduced by up to 83% in the long term	Yes	No	Common: weight gain; bloating; breast tenderness; headaches; acne (but all are usually minor and transient) Rare: depression
Injected or implanted progestogen	Prevents proliferation of the endometrium	Injected intramuscularly every 12 weeks; a subdermal implant is also available that is licensed for 3 years	Bleeding is likely to stop completely	Yes	No	Common: weight gain; irregular bleeding; amenorrhoea; premenstrual-like syndrome (including bloating, fluid retention, breast tenderness) Less common: small loss of bone mineral density, largely recovered when treatment is discontinued
Gonadotrophin-releasing hormone analogue (GnRH-a)	Stops production of estrogen and progesterone	Monthly injection (for 3–6 months); if used for more than 6 months, 'add-back' therapy is recommended	Bleeding stopped completely in 89% of women	No	No	Common: menopausal-like symptoms (such as hot flushes, increased sweating, vaginal dryness) Less common: osteoporosis, particularly trabecular bone with longer than 6 months' use

9 Surgery as first-line treatment for HMB

Introduction

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

A summary of all surgical treatment options for HMB is given in Table 9.1 at the end of this chapter.

9.1 Surgery as first-line treatment for HMB

9.1.1 Review on surgery as first-line treatment for HMB

Overview of evidence

One systematic review and one subsequent RCT were identified. Further detail is provided in evidence table 9.1 and Figure 9.1.

Surgery as first-line treatment

One systematic review ($n=821$) undertaken in 2006 that included eight RCTs 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 the time) and surgery diminished over time until, by 5 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 10.6 (95% CI 5.3 to 21.3) in favour of surgery, by 2 years ($n=173$) OR 2.39 (95% CI 1.21 to 4.70) in favour of surgery, and by 5 years ($n=140$) OR 1.99 [95% CI 0.84 to 4.73] with no statistical difference between the groups. The figures for patient satisfaction were: at 4 months ($n=183$) OR 8.28 (95% CI 4.29 to 15.97) in favour of surgery, by 2 years ($n=173$) OR 2.83 [95% CI 1.46 to 5.50] in favour of surgery, and by 5 years ($n=140$) OR 1.69 (95% CI 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 2 years follow-up ($n=236$) OR 0.12 (95% CI 0.06 to 0.22) in favour of surgery and by 5 years follow-up ($n=140$) OR 0.11 (95% CI 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.[325] [EL=1++]

Six other RCTs were included in the review that compared LNG-IUS with surgery (hysterectomy, ablation) in secondary care settings, with the conclusion that the treatments were equivalent. The figures showed that objective measurement of MBL at 12 months was in favour of surgery (one RCT, $n=223$, OR 25.7 [95% CI 1.5 to 440.0]). Also, the subjective measurement of MBL at 12 months was in favour of surgery (three RCTs, $n=189$, OR 3.99 [95% CI 1.53 to 10.38]). However, results from HRQoL 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 [95% CI 1.65 to 17.69]), social

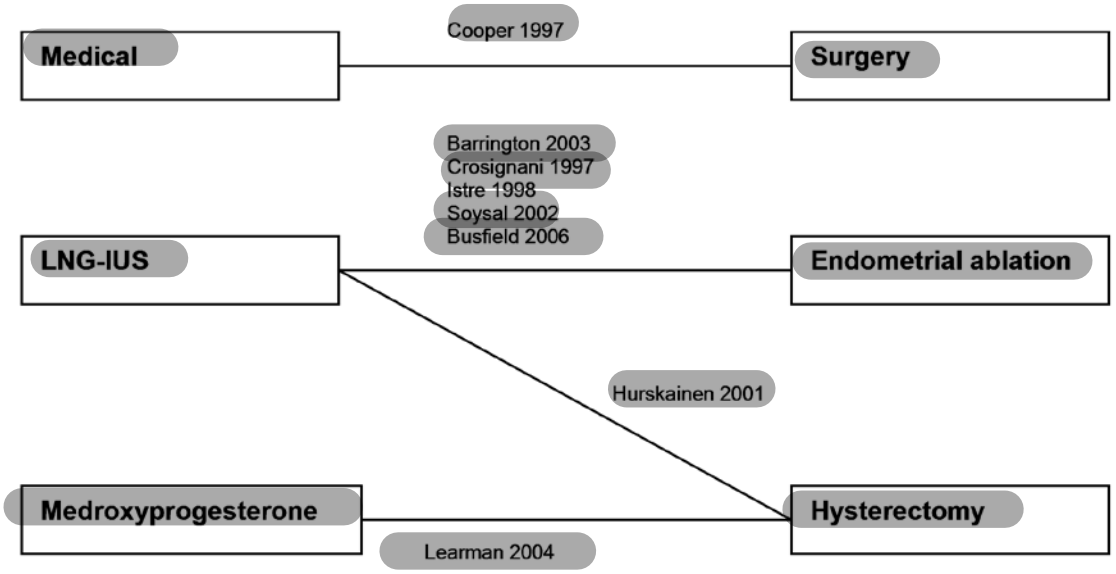


Figure 9.1 RCT evidence base on medical versus surgical interventions for HMB; trials comparing treatments are positioned along the line linking them[104,118,119,260,263,270,327,328]

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 to 0.49]).[325] [EL = 1++]

The review concluded that 'surgery reduces menstrual bleeding at one year more than pharmaceutical treatments, but LNG-IUS appears equally beneficial in improving quality of life and may control bleeding as effectively as conservative surgery over the long term. Oral medication suits a minority of women long term'.[325] [EL = 1++]

Further information on individual RCTs is available in evidence table 9.1.[119,243,260,263,264,266,268,270,326]

9.1.2 Evidence statements on surgery as first-line treatment for HMB in secondary care

One systematic review was available. The review showed 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 [95% CI 0.84 to 4.73]) in favour of surgery). However, this result may be due to nearly 90% of the pharmaceutical group undergoing surgery during the follow-up period. In one RCT included in the review (where LNG-IUS was not available), the results showed that women who underwent immediate surgery had statistically higher HRQoL at 5 years than those who underwent surgery after failed pharmaceutical treatment. The review did not examine how the presence of fibroids influenced outcomes. While surgery has an advantage over pharmaceutical treatment in terms of outcome, this does not take into account the reversible nature of pharmaceutical treatment compared with surgery. Further detail is provided in evidence table 9.1.

9.1.3 GDG interpretation of evidence on surgery as first-line 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 in controlling MBL, as shown by RCT evidence. However, the GDG discussion focused on the high level of subsequent surgery associated with pharmaceutical interventions, and on data suggesting that women who delay having surgery

Table 9.1 Surgical options for treating HMB; discuss the risks and benefits of each option with the woman and provide information and support to aid decision making;. offer counselling if the decision impacts on fertility

Indication	Types of surgery	What is involved?	How does it work? (information to aid discussion with the woman)	Effect on menstrual bleeding	Will it impact on future fertility?	Possible unwanted outcomes
Women whose bleeding is having a severe impact on quality of life and who do not want to remain fertile Normal size uterus and small fibroids	Second-generation endometrial ablation procedures: microwave endometrial ablation (MEA) and thermal balloon endometrial ablation (TBEA)	In MEA a probe is inserted into the uterus through the vagina and cervix. This probe produces microwaves that destroy the lining of the womb. [summarized from UNG for TA 78] Endometrial thinning or scheduling of surgery for the postmenstrual phase is needed In TBEA a deflated balloon is moved into the uterus through the vagina and cervix. Once in place, the balloon is filled with a heated liquid. The heat destroys the lining of the womb. [taken from TA 78] Endometrial thinning is not required	Removing the womb lining should stop heavy bleeding. In some women the lining grows back and the surgery may need to be repeated Effective contraception should be used after this procedure	Clinically relevant reductions in bleeding, and improvements in quality of life Endometrial ablation and resection techniques are slightly less effective than hysterectomy	Yes	Common: vaginal discharge; increased period pain or cramping (even if no further bleeding); need for additional surgery Less common: infection
Women who have heavy bleeding and other treatments have failed or are inappropriate, they don't want to remain fertile, they want their periods to stop, or they have large fibroids	Hysterectomy First line: vaginal	The uterus, cervix and/or ovaries are removed	Removing the uterus means periods stop permanently	No bleeding	Yes	Common: infection Less common: intra-operative haemorrhage; damage to other abdominal organs, such as the urinary tract or bowel; urinary dysfunction – frequent passing of urine and incontinence *With oophorectomy at the time of hysterectomy:* Common: menopausal-like symptoms
	Hysterectomy Second line: abdominal (total and sub-total)	The uterus and/or cervix and/or ovaries are removed	Removing the uterus means periods stop permanently	No bleeding		
	Hysterectomy Morbidly obese/ oophorectomy: laparoscopic		Removing the uterus means periods stop permanently	No bleeding		
	Oophorectomy	One or both ovaries are removed	Ovaries removed when there is an increased risk of ovarian or breast cancer	None		
Heavy bleeding and large fibroids	Uterine artery embolisation (UAE)	Small particles are injected into the blood vessels that take blood to the uterus [taken from IP 94]	The blood supply to the fibroids is blocked and this causes them to shrink [taken from IP 94]	It may reduce bleeding	No, fertility is potentially retained	Common: persistent vaginal discharge; post-embolisation syndrome – pain, nausea, vomiting and fever (not involving hospitalisation) Less common: need for additional surgery; premature ovarian failure, particularly in women over 45 years old; haematoma
	Myomectomy	There are a number of routes: abdominal, vaginal, laparoscopic and hysteroscopic. Choice of route is determined by the size and position of the fibroids. Further surgery may be needed in the future	Fibroids are removed	It may reduce bleeding	No, fertility is potentially retained	Less common: adhesions (which may lead to pain and/or impaired fertility); need for additional surgery; recurrence of fibroids; perforation (hysteroscopic route); infection

'Common' unwanted effects are those that may be experienced by 1 in 100 women; 'less common' unwanted effects are those experienced by 1 in 1000 women; rare unwanted effects are not shown here.

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

Recommendations on surgery as first-line treatment for HMB in secondary care

Endometrial ablation may be offered as an initial treatment for HMB after full discussion with the woman of the risks and benefits and of other treatment options. [A]

Hysterectomy should not be used as a first-line treatment solely for HMB. [D(GPP)]

To allow the reader to see all the recommendations relating to a specific treatment in one place, the above recommendation on ablation has been repeated in Section 10.2 and that on hysterectomy in Chapter 12.

10 Non-hysterectomy surgery for HMB

10.1 Indications for non-hysterectomy surgery or interventional radiology

Clinical indications for referral for surgery or interventional radiology are where the impact of symptoms cannot be treated by medical means, or the woman requests referral to a more specialist clinician to discuss these options to avoid hysterectomy. Women's preferences are their opinions and beliefs with regard to the outcome that they want from treatment, and what type of treatment they are willing to accept in order to achieve that outcome.

10.1.1 Review on indications for non-hysterectomy surgery or interventional radiology

Overview of available evidence

No RCTs or systematic reviews of RCTs were identified and thus reviews of observational studies were included. In total, three primary studies were included. Further information is provided in evidence tables 10.1 and 10.2.

Indications for non-hysterectomy surgery or interventional radiology

A prognostic study ($n = 130$) on women who had undergone thermal balloon endometrial ablation (TBEA) found that only endometrial thickness and the position of the uterus impacted on the success of the outcome. These factors should thus be taken into account prior to undertaking TBEA.[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.[244] [EL = 3]

Another patient preference study ($n = 221$) examined women's priorities for treatment of menorrhagia and found that 'stops periods for good' and 'back to usual activities as soon as possible' were the two most important wishes of women.[245] [EL = 3]

10.1.2 Evidence statements on indications for non-hysterectomy surgery or interventional radiology

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. Further information is provided in evidence tables 10.1 and 10.2.

10.1.3 GDG interpretation of evidence on indications for non-hysterectomy surgery or interventional radiology

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

Recommendations on indications for non-hysterectomy surgery or interventional radiology

These have been added to Section 10.2 of this chapter and Section 11.3 of Chapter 11.

10.2 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 pharmaceutical treatment for HMB 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 completely stopping MBL.

The first procedures to be developed (first generation) involved distending the uterine cavity with fluid and either resecting the tissue with an electrosurgical loop, which is known as transcervical resection of the endometrium (TCRE), and/or a heated rollerball is used to burn away the tissue (REA). All these methods are performed under direct visualisation and outcome is dependent on the skill and experience of the surgeon. They all have a risk of absorption of the fluid used to distend the uterus into the blood stream, but the degree varies from one method to another.

As these methods are relatively difficult to learn, new methods have been developed. These second-generation methods are in general not performed under direct vision of the uterine cavity, and are easier to learn and safer to use. This group include thermal balloon endometrial ablation (TBEA), microwave endometrial ablation (MEA), hydrothermablation, bipolar radiofrequency endometrial ablation and endometrial cryotherapy.

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

10.2.1 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 owing to the availability of good RCT evidence. Further information is provided in evidence tables 10.3 and 10.4 and in Figure 10.1.

Endometrial ablation versus other treatments

A systematic review in 1999 (five RCTs) compared hysterectomy with endometrial ablation. The review found that, in terms of reduction in MBL, hysterectomy provided greater reductions (at 12 months (three studies, $n=440$) OR 0.12 [95% CI 0.06 to 0.25]). Patient satisfaction also favoured hysterectomy (at 12 months (three studies, $n=519$) OR 0.46 [95% CI 0.24 to 0.88] and at 24 months (three studies, $n=354$) OR 0.31 [95% CI 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 ($P=0.007$), which were all in favour of hysterectomy. However, endometrial ablation techniques required less time to undertake ((five studies, $n=706$) WMD = −23.06 [95% CI −23.80 to −22.32] in favour of ablation/resection), shorter hospital stays ((five studies, $n=706$) WMD = −4.91 [95% CI −4.95 to −4.87]) and fewer adverse events. Of the 13 types of adverse event 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 7.33 [95% CI 4.18 to 12.86]). The review concluded that ablation/resection is an alternative to hysterectomy but is less effective at reducing MBL and improving satisfaction. However, ablation/resection does lead to shorter surgery and fewer complications.[330] [EL= 1++]

A number of RCTs comparing ablation with LNG-IUS and other pharmaceutical treatments were also identified. These are reviewed in Chapter 8.[260,263,266,268,270,331–333]

Endometrial ablation/resection

A systematic review undertaken as part of a health technology appraisal report (two reviews and ten RCTs, search date 2002) examined the effectiveness and safety of MEA and TBEA for HMB.

The review found that 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. It concluded that both MEA and TBEA were equivalent to first-generation ablation techniques.[334] [EL = 1+]

A second systematic review (19 RCTs, search date 2005) compared the various ablation techniques with one another for treatment of HMB. Only limited differences were found when comparing one ablation method with another. The comparisons undertaken in this review are outlined below, but only the statistically significant differences between treatments are reported.[335] [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 6.0 [95% CI 1.7 to 20.9]. There was no difference between methods for amenorrhoea rates, satisfaction, HRQoL or complications.

Vaporising electrode ablation versus TCRE

One RCT ($n = 91$) was identified. TCRE was more likely to be difficult to perform (OR 0.25 [95% CI 0.09 to 0.73]), had greater fluid deficit (WMD 258 ml [95% CI 174 to 342]) and took longer to perform (WMD = +1.5 minutes [95% CI 0.35 to 2.65]). There were no differences between methods for amenorrhoea rates, satisfaction or HRQoL. However, it is unclear how similar vaporising electrode ablation is to REA, and whether the two should be differentiated.

REA versus TCRE

There was no difference between techniques in terms of future hysterectomy or re-surgery at 2 and 5 years follow-up.

Thermal laser ablation versus TCRE

One RCT ($n = 111$) was identified. Amenorrhoea rates were higher at 1 and 3 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 2.0 to 10.5] at 3 years). The mean length of surgery was shorter in the thermal group (WMD = 9.3 minutes [95% CI 11.4 to 7.2]). There were no differences between groups for menorrhagia, re-surgery, complications or satisfaction.

Hydrothermablation versus REA

One RCT ($n = 269$) was identified. Hydrothermablation patients were more likely to have local than general anaesthesia (OR 2.9 [95% CI = 1.6 to 5.1]) and were less likely to experience haematometra (OR 0.18 [95% CI 0.03 to 0.93]) but were more likely to have abdominal pain (OR 1.9 [95% CI 1.1 to 3.1]) and nausea (OR 3.7 [95% CI 1.5 to 9.0]).

Cryoablation versus REA

Two RCTs ($n = 279$) were identified. Women in the cryoablation group were less likely to have amenorrhoea at 1 year (OR 0.3 [95% CI 0.2 to 0.6]) but more likely to have local than general anaesthesia (OR 13.2 [95% 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 operation time with TCRE was longer (WMD 18.7 minutes [95% CI 16.8 to 20.7]). The electrode group was more likely to have local than general anaesthesia (OR 15.9 [95% CI 10.1 to 25.1] and less likely to have cervical tears or lacerations (OR 0.11 [95% CI −0.01 to 0.90]). There were no differences between groups in amenorrhoea rates, complications rates, 12 month PBAC, satisfaction rates or need for hysterectomy.

MEA versus TCRE plus REA

One RCT ($n = 322$) was identified. At 2 years follow-up, microwave was more satisfactory and acceptable than TCRE (OR 1.9 [95% CI 1.1 to 3.3] and OR 2.7 [1.1 to 6.8], respectively). At 5 years follow-up the difference was maintained (OR 2.3 [95% CI 1.2 to 4.3] and OR 3.7 [95% CI 1.3 to 10.1], respectively). The hysterectomy rate following MEA was significantly lower (18% versus 28%). In addition, odds of haemorrhage were lower in the microwave group (OR 0.14

[95% CI 0.02 to 0.80]). However, equipment failure rates (OR 4.07 [95% CI 1.1 to 15.0]), vomiting (OR 4.0 [95% CI 1.4 to 11.7] and uterine cramping (OR 1.7 [95% CI 1.1 to 2.8]) were greater in the MEA group. There were no differences in other outcomes or in the same outcomes at different time periods.

TBEA versus REA

One RCT ($n=239$) was identified. Amenorrhoea was less likely with TBEA at 12 and 36 months (OR 0.60 [95% CI 0.33 to 0.96] and OR 0.50 [95% CI 0.25 to 0.97], respectively) but there were no differences at 24 months and 5 years. At 5 years, odds of satisfaction with treatment were lower in the balloon group (OR 0.13 [95% CI 0.02 to 0.94]), and complications were more likely with TBEA than with REA. Duration of surgery was lower in the balloon group (WMD 20.8 minutes [95% CI 19.2 to 22.5]). Other outcomes showed no differences at 12, 24 and 36 months.

TBEA versus TCRE

One RCT ($n=82$) was identified. TBEA was quicker (WMD 13 minutes [95% CI 10.8 to 15.2), mean intra-operative blood loss was lower (WMD −81.8 ml [95% CI −70.3 to −93.3]) and satisfaction was greater at 24 months (OR 7.2 [95% CI 1.4 to 35.9]) when compared with TCRE.

TBEA versus laser ablation

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 radiofrequency endometrial ablation versus TBEA

One RCT ($n=126$) was identified. Amenorrhoea was more likely in the bipolar radiofrequency group (OR 7.4 [95% CI 3.8 to 14.4]) and women in the bipolar radiofrequency group were more likely to be satisfied with treatment outcome at 12 months (OR 3.0 [95% 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.'

Additional or subsequent RCTs

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 radiofrequency 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 HRQoL.[336] [EL = 1+]

In addition, owing to the debate within the GDG about the conclusions made by some of the reviews, it was necessary to assess the individual RCTs on which they were based.[102,103,243,336–359] The results of this review are reflected in the recommendations made by the GDG.

Additional comparative studies are also available in evidence tables 10.3 and 10.4.[101,360–395]

Health economics

One economic evaluation met the criteria for inclusion (details of the study are provided above).[334] The evaluation compared MEA and TBEA with TCRE, REA and hysterectomy. A state-transition (Markov) model was used, and assumed a hypothetical cohort of 1000 patients for a period of 10 years. The average age of women entering the model was 42 years. TBEA dominates all other ablation techniques. When compared with MEA, TBEA gives a similar number of quality-adjusted life years (QALYs) across the cohort (TBEA 8360.77, MEA 8360.70) but at a slightly lower cost

(TBEA £1,323,925, MEA £1,448,470). When compared with TCRE, REA and TCRE and REA in combination, both TBEA and MEA produce more QALYs at a lower cost. When compared with hysterectomy, MEA and TBEA are both less costly but provide fewer QALYs. Hysterectomy results in 8774.34 QALYs at a cost of £2,320,512. The incremental cost-effectiveness ratio for hysterectomy compared with TBEA is £2,410 per QALY, and compared with MEA is £2,108 per QALY. The study concluded that hysterectomy is cost-effective compared with MEA and TBEA.

The robustness of the study results was 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 with TCRE, REA 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.

10.2.2 Review of endometrial thinning as pre-treatment before endometrial ablation

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

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, that danazol was less effective than GnRH-a and only slightly better than placebo, and 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 the authors at the time of publication.[396] [EL = 1+]

Information from individual RCTs included in the review can be found in evidence tables 10.3 and 10.4.[397–399]

One RCT ($n = 210$) compared MEA undertaken in the postmenstrual phase with endometrial ablation undertaken with hormonal pre-treatment (danazol 200 mg b.d., depot goserelin 3.6 mg 5 weeks prior to surgery). The study found no statistically significant difference between the groups in relation to women's outcomes (patient satisfaction at 12 months: postmenstrual 92.5% versus drug group 88.4%).[400] [EL = 1++]

A second RCT ($n = 90$) of women with menorrhagia showed that pre-treatment with danazol or Decapeptyl® (triptorelin) before hydrothermablation had no effect on outcome compared with 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).[401] [EL = 1–]

A third RCT ($n = 30$) comparing pre-treatment with Decapeptyl 3.75 mg at 4–6 weeks prior to treatment with 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.[402] [EL = 1–]

A fourth RCT ($n = 50$) examining the use of depot medroxyprogesterone acetate (DMPA) pre-treatment for women undergoing endometrial resection found no differences in outcome or duration of procedure, but level of fluid deficit did favour the pre-treatment group (DMPA 690 ml, control 476 ml ($P < 0.005$)).[403] [EL = 1–]

Health economics

A systematic review identified one study that met the inclusion criteria.[404] The study retrospectively examined the results of a randomised trial ($n = 160$) comparing preoperative medical endometrial thinning in women undergoing endometrial ablation for menorrhagia. Treatments compared were goserelin (GnRH-a) and danazol for either 4 or 8 weeks and outcomes were measured by the differential rate of amenorrhoea in women 24 weeks and 2 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 2 years follow-up, although 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 effective) to an incremental result of £201 per additional woman with amenorrhoea when treated with goserelin. These results should be interpreted with caution, given the sample size, the number of women unavailable at long-term follow-up and the issue of whether an appropriate outcome has been selected.

One study ($n = 210$) compared MEA performed during the postmenstrual phase in an outpatient setting under local anaesthetic with standard MEA in a day-case setting after drug preparation of the endometrium. Outcomes measured were acceptability of, and satisfaction with, treatment. Health-related quality of life was measured using the SF-12 scale (version 1). There were no statistically significant differences in SF-12 scores, and utility values were not calculated. Mean costs to the health service of the postmenstrual group were £444 and for the drug preparation group £568. Costs to the woman were also measured but there was no significant difference between the postmenstrual (£190) and drug preparation (£199) groups.[400]

10.2.3 Evidence statements on endometrial ablation/resection

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

Results from three reviews and one RCT show that endometrial ablation and resection methods produce 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 found that MEA is superior to TCRE in terms of satisfaction at 5 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 with 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 MEA are slightly more than for TBEA, with no meaningful difference in number of QALYs. Both MEA and TBEA are less costly and resulted in slightly more QALYs than either TCRE or REA.

When compared with hysterectomy, both TBEA and MEA are less costly, but result in slightly fewer QALYs. The incremental cost-effectiveness ratio for hysterectomy compared with 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.

10.2.4 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 minimising the impact of surgery.

With regard to endometrial ablation, the GDG examined the individual comparisons of techniques. In the majority of RCTs the techniques were found to be largely equivalent. However, in one recent long-term follow-up study it was found that MEA was superior to TCRE in terms of women's satisfaction.

The GDG highlighted that there was no good evidence comparing the various second-generation techniques, and therefore conclusions had to be based on extrapolated evidence from comparisons between first- and second-generation techniques. Further information is provided in evidence tables 10.3 and 10.4.

NICE has produced a technology appraisal (No. 78) on MEA and TBEA, which concludes:[405]

'Based on the available evidence on the effectiveness of TBEA and MEA, the Committee concluded that TBEA and MEA are likely to be as effective as first-generation EA techniques in terms of reducing abnormal menstrual bleeding patterns in women with HMB. However, the Committee considered that there was not sufficient evidence to differentiate between TBEA and MEA in terms of their overall effectiveness when all potential outcomes were considered jointly.'

Fluid-filled TBEA and MEA are recommended as treatment options for women with HMB in cases where it has been decided (by the woman and the clinician responsible for her treatment) that surgical intervention is appropriate for the management of the condition.[405]

For HMB, the choice of surgical treatment should be made jointly by the woman and the clinician responsible for treatment. The decision should be made after an informed discussion taking into account the desired outcome of the treatment (such as reduced menstrual bleeding or complete cessation of menstrual bleeding (amenorrhoea)), the relative benefits of all other treatment options and the adverse events associated with them, as well as the clinical condition, anatomical suitability and preferences of the woman.[405]

The GDG has fully acknowledged the recommendations made in the technology appraisal. The guideline developers have sought to consider a number of second-generation techniques in addition to those in the technology appraisal, and in addition have provided details of when first- and second-generation techniques or other surgical options would be most appropriate. These issues are reflected in the recommendations made by the GDG.

NICE has also produced a number of interventional procedure documents relating to specific techniques of endometrial ablation:[406–408]

- 'Current evidence on the safety and efficacy of free fluid thermal endometrial ablation appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.'[406]
- 'Current evidence on the safety and efficacy of impedance-controlled bipolar radiofrequency ablation for menorrhagia appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.'[407]
- 'Limited short-term evidence on the safety and efficacy of endometrial cryotherapy for menorrhagia appears adequate to support the use of this procedure in carefully selected patients provided that normal arrangements are in place for consent, audit and clinical governance.'[408]

NICE interventional procedures 6, 7, 51 and 104 on endometrial ablation are superseded by this guideline, as the techniques have been shown to be in routine use within the NHS and to be cost-effective. However, interventional procedure 157 on cryotherapy is not covered by this guideline as it is not in routine use within the NHS.

Recommendations on endometrial ablation/resection

Endometrial ablation should be considered where bleeding is having a severe impact on a woman's quality of life, and she does not want to conceive in the future. [C]

Endometrial ablation may be offered as an initial treatment for HMB after full discussion with the woman of the risks and benefits and of other treatment options. [A]

Women must be advised to avoid subsequent pregnancy and on the need to use effective contraception, if required, after endometrial ablation. [D(GPP)]

Endometrial ablation should be considered in women who have a normal uterus and also those with small uterine fibroids (less than 3 cm in diameter). [A]

In women with HMB alone, with uterus no bigger than a 10 week pregnancy, endometrial ablation should be considered preferable to hysterectomy. [A]

All women considering endometrial ablation should have access to a second-generation ablation technique. [D(GPP)]

Second-generation ablation techniques should be used where no structural or histological abnormality is present. [A] The second-generation techniques recommended for consideration

are as follows. Providers should ensure that when purchasing any of these they buy the least expensive available option:*†‡§

- impedance-controlled bipolar radiofrequency ablation (formerly NICE interventional procedure guidance 104)
- fluid-filled thermal balloon endometrial ablation (TBEA) (formerly NICE interventional procedure guidance 6)
- microwave endometrial ablation (MEA) (formerly NICE interventional procedure guidance 7)
- free fluid thermal endometrial ablation (formerly NICE interventional procedure guidance 51).

In TBEA, endometrial thinning is not needed. [D(GPP)]

In MEA, scheduling of surgery for postmenstrual phase is an alternative to endometrial thinning. [A]

First-generation ablation techniques (for example, rollerball endometrial ablation (REA) and transcervical resection of the endometrium (TCRE)) are appropriate if hysteroscopic myomectomy is to be included in the procedure. [D(GPP)]

Research recommendations on endometrial ablation/resection

- Where evidence is not available on endometrial thinning prior to different ablative techniques, it is recommended this research be undertaken.
- An RCT investigation of the clinical effectiveness and cost-effectiveness of the various second-generation ablation techniques against one another.
- An opportunity to evaluate any new endometrial ablation techniques within an RCT format.

10.3 Dilatation and curettage

Dilatation and curettage is mainly used in HMB as a diagnostic tool, as it allows for testing of the endometrial material collected.

10.3.1 Review of dilatation and curettage

Overview of available evidence

Only one observational study was identified and there were no systematic reviews or RCTs. Further information is provided in evidence table 10.5.

Dilatation and curettage

The observational study ($n = 22$) showed graphically (no figures provided) that MBL was reduced for 1 month after dilatation and curettage but then returned to previous levels.[409] [EL = 2–]

10.3.2 Evidence statements on dilatation and curettage

Limited evidence is available on the use of therapeutic dilatation and curettage for HMB, but the one study that was identified showed that any effect was temporary.

* NICE have produced 'Fluid-filled thermal balloon and microwave endometrial techniques for heavy menstrual bleeding. NICE technology appraisal guidance 78' on TBEA and MEA.

† This clinical guideline supersedes the following NICE interventional procedure guidances: 'Balloon thermal endometrial ablation. IPG 6', 'Microwave endometrial ablation. IPG 7', 'Free fluid endometrial ablation. IPG 51' and 'Impedance-controlled bipolar radiofrequency ablation for menorrhagia. IPG 104'. However, 'Endometrial cryotherapy for menorrhagia. NICE interventional procedure guidance 157' is not covered by this guideline.

‡ Reference should be made to the limits on uterus size given by the manufacturer of the endometrial ablation device.

§ 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').

10.3.3 GDG interpretation of evidence on dilatation and curettage

Given the limited evidence, the GDG recommendation was based on clinical experience. Further information is provided in evidence table 10.5.

Recommendations on dilatation and curettage

Dilatation and curettage should not be used as a therapeutic treatment. [C]

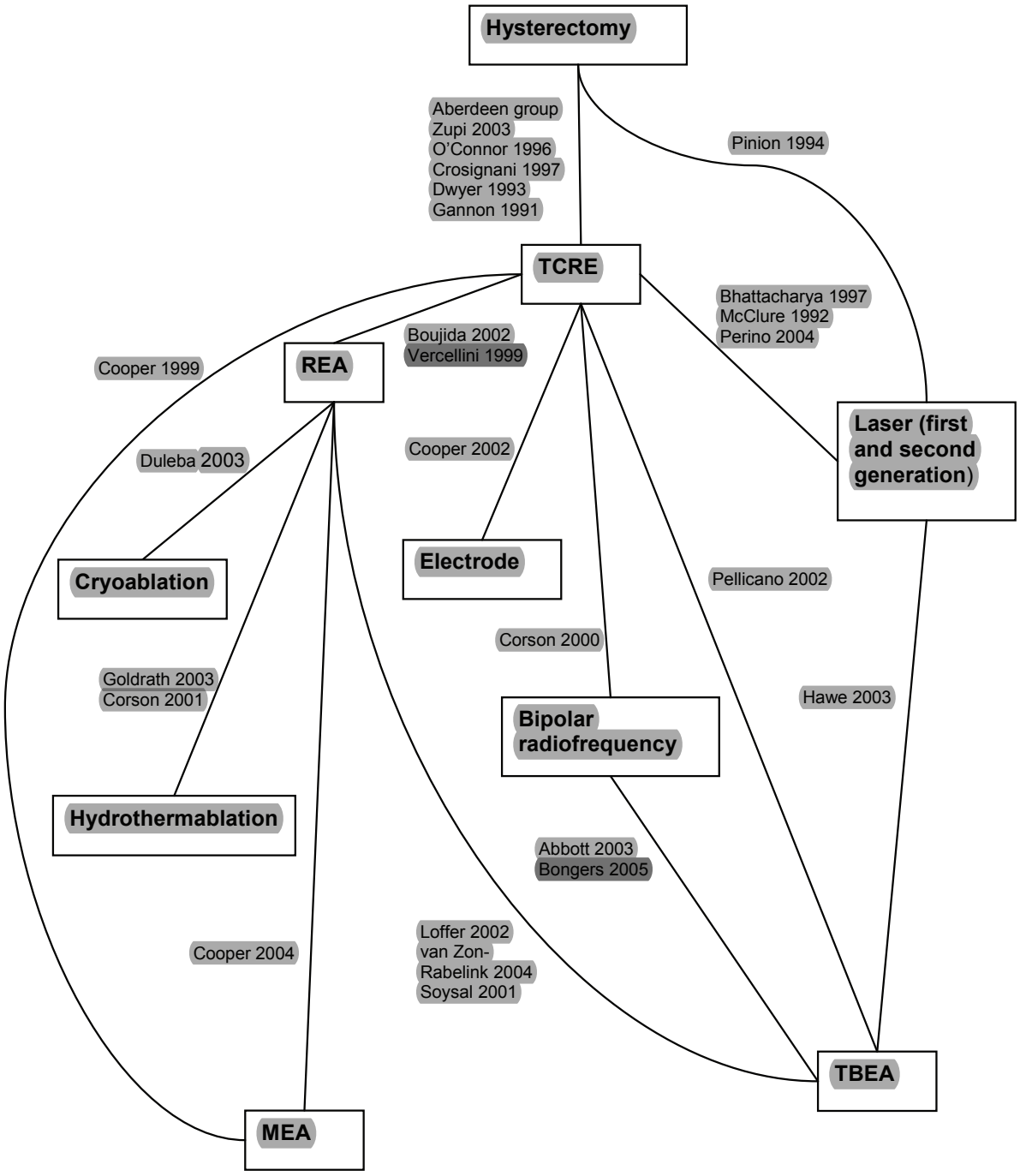


Figure 10.1 RCT evidence base for comparisons between endometrial ablation techniques for HMB; trials comparing treatments are positioned along the line linking them[331,333,337–339,342–349,351,353,356–358,382,410–415]

11 Further interventions for uterine fibroids associated with HMB

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 through a catheter inserted into them via the femoral artery. 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. It can be performed by laparotomy, laparoscopically or hysteroscopically. The choice of route is determined by the size and position of the fibroid(s). A concern with the use of myomectomy is that uterine fibroids may reappear and require further surgery.

11.1 Uterine artery embolisation

11.1.1 Review of UAE for treating HMB

Overview of available evidence

One systematic review of three RCTs was identified. One subsequent RCT was identified. Further information is provided in evidence tables 11.1 and 11.2.

UAE versus hysterectomy

One review was identified (three RCTs) comparing UAE with hysterectomy or myomectomy. The review identified all the available RCT evidence on UAE.[416] [EL = 1+]

For the RCT studies comparing UAE with hysterectomy, the review reported a shorter duration of procedure (WMD −16.4 minutes [95% CI −26.0 to −6.8]), less intra-procedure blood loss (WMD −405 ml [95% CI −513 to −298]), shorter length of hospital stay (WMD −3.27 days [95% CI −3.77 to −2.77]), less need for blood transfusion (OR 0.04 [95% CI 0.00 to 0.33]) and quicker resumption to normal activities (WMD −26.7 days [95% CI −36.2 to −17.2]) in the UAE group compared with the hysterectomy group. There was no significant difference between the two groups in terms of 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]) or 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]).[416]

Further information on individual RCTs can be found in evidence table 11.1.[417–423]

Health economics

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 GHQ 28 scores. Measurements were taken prior to treatment, at 1 month following treatment and at 12 months following treatment. No statistically significant differences

were 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 £1,685.36 (95% CI £1,465.72 to £1,905.00) compared with surgery at a mean cost of £2,566.87 (95% CI £2,263.73 to £2,870.01). 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 (one RCT) showed that the results favoured UAE in the duration of procedure (WMD −34.5 minutes [95% CI −48.7 to −20.3]), length of hospital stay (WMD −1.60 days [95% CI −2.47 to −0.73]) and duration to full recovery (WMD −16.4 days [95% CI −21.2 to −11.6]). However, re-intervention rates favoured the myomectomy group (OR 8.97 [95% CI 1.79 to 44.95]). There was no significant difference between the 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 1 week (OR 0.11 [95% CI 0.01 to 2.08]), readmission to hospital (OR 2.29 [95% CI 0.20 to 26.58]) or total relief of all fibroid-related symptoms at 6 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+]

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, owing 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 owing to uterine fibroids compared UAE with surgery (hysterectomy or myomectomy). At 12 months follow-up the study found no differences between the groups in SF-36 scores, EuroQol EQ-5D scores, complications or adverse events. However, the symptom score at 12 months was in favour of surgery ($P = 0.03$), as was the need for subsequent treatment (13% versus 4%).[417] [EL = 1+]

A cohort study ($n = 111$) compared outcomes in women undergoing abdominal myomectomy (AM) ($n = 44$) or UAE ($n = 97$) for symptomatic fibroids. At 14 months follow-up there was a significant reduction in menorrhagia in the UAE group (92% versus 64%, $P < 0.05$) but not in pain (52% versus 74%, non-significant). Treatment of pain symptoms was significantly more successful with AM than UAE (91% versus 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 days versus 0 days and 39 days versus 8 days, respectively, $P < 0.05$). The study concluded that UAE is less invasive and a safer treatment than AM in women with symptomatic fibroids.[424] [EL = 2+]

A cohort study compared long-term outcomes of UAE ($n = 51$) and AM ($n = 30$) in women with symptomatic fibroids. It reported that further invasive therapy was significantly more likely in the UAE group than the AM group (29% versus 3%, OR 12.5 [95%CI 1.4 to 110.1]) at 3–5 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 ($P = 0.06$).[425] [EL = 2+]

A prospective cohort study ($n = 146$) compared UAE with myomectomy. The study found that UAE was associated with greater improvement in symptoms and HRQoL than myomectomy, and this was achieved with fewer adverse effects.[426] [EL = 2+]

At the time of submission of the guideline to NICE, the GDG was aware of one unpublished study, the HOPEFUL study, which is a large retrospective analysis of UAE compared with hysterectomy.

Non-comparative studies

A prospective case series ($n=3160$) of women who had undergone UAE examined reported adverse events. Major in-hospital complications occurred in 0.66% of the women, and post-discharge major events occurred in 4.8% of the women within the first 30 days of surgery. The number of in-hospital events reported were: none, 2952; one event, 89; two events, 5. Of these events, 20 were defined as major and 74 as minor. Post-discharge adverse events ($n=2729$) reported were: none, 2019; one event, 519; two events, 128; three events, 49; four or more events, 14. Of these events, 135 were defined as major and 848 as minor.[427] [EL = 3]

Multivariate analysis showed that adverse events were significantly associated with the following factors: having had any prior procedure (OR 1.235, $P<0.001$), deep vein thrombosis 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'.[427] [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 (0 to 100; baseline, 6 months, 12 months; mean (SD)): 58.61 (20.82), 19.87 (18.61), 19.23 (17.94) ($P<0.001$) and HRQOL score (0 to 100; baseline, 12 months; mean (SD)): 46.95 (23.03), 86.68 (18.15) ($P<0.001$) based on the Uterine Fibroid Symptom and Quality of Life questionnaire. Subsequent pharmaceutical treatment, gynaecological interventions and unplanned accident and emergency 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.[428] [EL = 3]

Multivariate analysis showed that a greater improvement in symptom and HRQoL scores 12 months after UAE was likely to be associated with factors such as predominant presenting symptoms of HMB, leiomyoma size, submucosal leiomyoma and age. The study concluded that 'uterine embolisation results in substantial symptom improvement for most patients, with hysterectomy required in only 2.9% of patients in the first 12 months after therapy'.[428] [EL = 3]

Additional non-RCT studies can be found in evidence table 11.2.[429–456]

11.2 Myomectomy

A number of routes (abdominal, vaginal, hysteroscopic and laparoscopic) are used to perform myomectomy. The choice of route is decided by the size and location of the uterine fibroids, the size and shape of the vagina and the training and experience of the surgeon.

11.2.1 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 with UAE, and another comparing various types of myomectomy. A number of comparative observational studies were also identified. Further information is provided in evidence tables 11.3 and 11.4.

Abdominal myomectomy versus hysterectomy

A cohort study compared perioperative morbidity between women who underwent abdominal myomectomy ($n=197$) or abdominal hysterectomy ($n=197$). It reported no significant difference in overall morbidity between the two groups (39% versus 40%, OR 0.93 [95 CI 0.63 to 1.40]). There was significantly 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 perioperative morbidity between myomectomy and hysterectomy was detected. Myomectomy may be considered a safe alternative to hysterectomy.[457] [EL = 2+]

Abdominal myomectomy versus UAE

One RCT comparing UAE with myomectomy was identified and was summarised in the UAE review. The results favoured UAE in the duration of procedure (WMD −34.5 minutes [95% CI −48.7 to −20.3]), length of hospital stay (WMD −1.60 days [95% CI −2.47 to −0.73]) and duration to full recovery (WMD −16.4 days [95% CI −21.2 to −11.6]). 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 1 week (OR 0.11 [95% CI 0.01 to 2.08]), readmission to hospital (OR 2.29 [95% CI 0.20 to 26.58]) or total relief of all fibroid-related symptoms at 6 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+]

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A prospective cohort study ($n = 146$) compared UAE with myomectomy. The study found that UAE was associated with greater improvement in symptoms and HRQoL than myomectomy, and this was achieved with fewer adverse effects.[426] [EL = 2+]

Hysteroscopic myomectomy with and without endometrial ablation

This combined therapy is undertaken in order to control HMB, but performing endometrial ablation means that a woman's potential future fertility is lost compared with 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 versus 81% of women with no endometrial ablation (OR 0.18 [95% CI 0.05 to 0.63]). Bleeding was controlled in 90% of women who had complete removal of myoma versus 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 endometrial ablation, bleeding was controlled in 97% compared with 84% in women who had complete removal of myoma and no endometrial ablation (OR 0.19 [95% CI 0.04 to 0.87]). In women who had incomplete removal of myoma, bleeding was controlled in 92% in those who had concomitant endometrial ablation compared with 70% in those women who had no endometrial ablation (OR 0.20 [95% CI 0.02 to 1.79]). There was significant success in control of bleeding among women who had complete removal of myoma with endometrial ablation versus those who had incomplete removal of myoma with endometrial ablation (common OR 5.25 [95% CI 1.49 to 18.54]). There were no significant differences in the rates of subsequent hysterectomy between all of these groups. Endometrial ablation at the time of hysteroscopic myomectomy improves results in the control of bleeding.[458] [EL = 2+]

A comparative retrospective chart review ($n = 156$ women, 94 hysteroscopic submucous resection of uterine leiomyomas and 62 endometrial ablation with or without submucous resection) reported on the long-term effectiveness of these procedures. In women undergoing hysteroscopic

submucous resection of uterine leiomyomas, 24.5% reported late postoperative problems (recurrent abnormal bleeding, uterine rupture and pain) and 84% had not required further surgery by 9 years follow-up. Among the endometrial ablation group, 23% of women experienced recurrence of increased bleeding and 91% had not required further surgery by 6 years follow-up.[459] [EL = 2–]

Abdominal myomectomy versus combined abdominal myomectomy and uterine depletion

A non-randomised study compared outcomes of women who underwent myomectomy only ($n = 108$, Group 1) with those who underwent combined uterine depletion (double ligation of the uterine artery) and myomectomy ($n = 234$, Group 2) for the treatment of symptomatic fibroids. Although the operation time was significantly shorter in Group 1 (55 minutes versus 68 minutes, $P < 0.001$), there was significant reduction in intra-operative blood loss in Group 2 (250 ml versus 50 ml, $P < 0.001$). At 16 months follow-up, fibroids recurred in 19% in Group 1 and not at all in Group 2 ($P < 0.001$).[460] [EL = 2+]

Abdominal versus laparoscopic myomectomy

An RCT compared AM ($n = 65$) and laparoscopic myomectomy ($n = 66$) in women with subserous or intramural myomas. It reported a significantly higher incidence of febrile morbidity (>38 °C) in the abdominal group than in the laparoscopic group (26.2% versus 12.1%, $P < 0.05$). The mean drop in haemoglobin was more pronounced in the abdominal group (2.17 ± 1.57 g/dl versus 1.33 ± 1.23 g/dl, $P < 0.001$). There was no significant difference in mean operation times between the two groups but the postoperative hospital stay was shorter in the laparoscopic group.[461] [EL = 1–]

A retrospective chart review compared the results of open myomectomy ($n = 49$) with those of laparoscopic myomectomy ($n = 49$). The review reported lower morbidity and fewer complications in women undergoing laparoscopic myomectomy when compared with open myomectomy. The mean operation time was significantly shorter and mean blood loss higher in the open myomectomy group (133 minutes versus 264 minutes and 340 ml versus 110 ml, respectively). The mean hospital stay was shorter (5.6 days versus 0.6 days) and the overall frequency of adhesion was lower in the laparoscopic group.[462] [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% had a 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.[463] [EL = 3]

A case series ($n = 108$ women who underwent hysteroscopic resection of myomas) followed up women over 7 years. It reported a cumulative rate of 34% for myoma recurrence and a cumulative probability of recurrent menorrhagia of 30% at 3 years. Hysteroscopic myomectomy gave satisfactory control of menorrhagia and limited recurrence, but the effect on fertility is limited.[464] [EL = 3]

Additional information from non-comparative studies can be found in evidence table 11.4.[462,465–468]

Preoperative pharmaceutical 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 and 18 gestational weeks, or fewer than four myomas larger than 4 cm in diameter, or myomas less than 10 cm in diameter, or fibroid size/volume up to 238 ml).[469] [EL = 1+]

Pre- and postoperative haemoglobin and haematocrit were significantly improved by GnRH-a 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-a 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-a pre-treatment in myomectomy patients was equivocal and few data were available to assess change in postoperative fertility. The review concluded that the use of GnRH-a for 3–4 months prior to fibroid surgery reduces both uterine volume and fibroid size.

Detailed information from the individual RCTs included in the review can be found in evidence table 11.3.[470–480]

11.3 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.

Evidence statements on interventions for fibroids

Evidence from one systematic review of RCTs and a large number of observational studies showed 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 myomectomy (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 statistically significantly lower than those for surgery. Evidence from two RCTs and several observational studies showed that myomectomy improves symptoms associated with uterine fibroids, and that the various methods of myomectomy can be considered equivalent. Evidence was inconclusive about the advantages and disadvantages of myomectomy compared with other treatments. Further information is provided in evidence tables 11.1 to 11.4.

GnRH-a use in myomectomy depends on size, number and site of uterine fibroids. In women with multiple small uterine fibroids, use of GnRH-a could hamper surgery, whereas in women with a single large uterine fibroid GnRH-a use could ease surgery.

The NICE interventional procedure document (No. 94) on uterine artery embolisation for the treatment of fibroids is superseded by this guideline.

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 GDG highlighted that use of GnRH-a is contraindicated when undertaking UAE owing to the effect that it has on blood vessels that makes the procedure more difficult.

The GDG highlighted that the studies on which recommendations are based used MRI as a diagnostic method.

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 might be classified as unavoidable results of treatment rather

than complications. There is insufficient evidence on long-term complication and recurrence rates to make recommendations on these issues. The GDG also highlighted that other techniques are becoming available within a research setting, such as myolysis.

Recommendations on interventions for uterine fibroids

For women with large fibroids and HMB, and other significant symptoms such as dysmenorrhoea or pressure symptoms, referral for consideration of surgery or uterine artery embolisation (UAE) as first-line treatment can be recommended.* [D(GPP)]

UAE, myomectomy or hysterectomy should be considered in cases of HMB where large fibroids (greater than 3 cm in diameter) are present and bleeding is having a severe impact on a woman's quality of life. [C]

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

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

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

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

Prior to scheduling of UAE or myomectomy, the uterus and fibroid(s) should be assessed by ultrasound. If further information about fibroid position, size, number and vascularity is required, MRI should be considered. [D(GPP)]

Pre-treatment before hysterectomy and myomectomy with a gonadotrophin-releasing hormone analogue for 3 to 4 months should be considered where uterine fibroids are causing an enlarged or distorted uterus.‡ [A]

If a woman is being treated with gonadotrophin-releasing hormone analogue and UAE is then planned, the gonadotrophin-releasing hormone analogue should be stopped as soon as UAE has been scheduled. [D(GPP)]

Research recommendations on interventions for uterine fibroids

- What effect do UAE and myomectomy have on the long-term fertility of women?
- What are the psychosexual impacts of UAE and myomectomy?
- What are the long-term recurrence rates of fibroids after UAE or myomectomy?
- How does UAE affect 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?

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, the appropriate training and experience is required by clinicians.

* See 'Uterine artery embolisation for the treatment of fibroids', NICE interventional procedure guidance 94, www.nice.org.uk/IPG094.

† See 'Uterine artery embolisation for the treatment of fibroids', NICE interventional procedure guidance 94, www.nice.org.uk/IPG094.

‡ Check the Summary of Product Characteristics for current licensed indications. Informed consent is needed when using outside the licensed indications. This should be discussed and documented in the notes.

12 Hysterectomy

Introduction

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 from HMB. However, a number of treatments have emerged as alternatives to hysterectomy. This change in the management of HMB can be seen in the reduction in the number of hysterectomies undertaken for bleeding disorders in the UK, according to Hospital Episode Statistics (HES), from 24 355 in 1993 to 10 559 in 2002. Clearly, 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. It is undertaken when disease requires the ovaries to be removed, but is often carried out 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.

12.1 Indications for hysterectomy

Given that there are now a number of treatment options for HMB that do not involve the removal of the uterus, it is important that the indications for the use of hysterectomy are clearly defined. Indications for surgery should include physical, psychological and social factors.

12.1.1 Review on indications for hysterectomy

Overview of available evidence

One guideline and five observational studies were included in the review. Further information is provided in evidence tables 12.1 to 12.3.

Indications for hysterectomy

One evidence-based guideline on indications for hysterectomy stated that it should only be considered in cases of dysfunctional uterine bleeding (DUB) after investigations had been undertaken to establish cause of bleeding, pharmaceutical treatment had failed or been refused by the woman, and the woman had been made aware of all alternative treatment options. For situations where myomas were present the indications were the same as for DUB, but prophylactic use of hysterectomy is indicated if myomas are growing rapidly to a point where the outcome of surgery may be affected.[481] [EL = 2+]

A consensus statement based on a Delphi process undertaken with 17 gynaecologists, outlined the main indications for hysterectomy. In relation to hysterectomy for HMB-related symptoms, the study made clear recommendations:

- hysterectomy should only be considered after thorough investigation of the cause of HMB
- surgery for DUB is only indicated when it is causing anaemia and major impairment
- surgery for myomas associated with HMB is indicated when it causes anaemia and/or major impairment.[482] [EL = 4]

A prognostic study ($n = 236$) of women who underwent either hysterectomy or were treated with LNG-IUS showed that age and presence of fibroids did not affect outcomes at 12 months.

However, presence of objective menorrhagia (>80 ml) did affect outcome, with those women who had menorrhagia having better outcomes with hysterectomy and those without menorrhagia having better outcomes with LNG-IUS. This suggests that the level of MBL should be assessed prior to surgery.[483] [EL = 2+]

A patient preference study ($n = 96$) assessing women's reasons 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.[244] [EL = 3]

A second patient preference study ($n = 180$) identified women's main reasons for rejecting hysterectomy (the main reason being that hysterectomy is a major operation), and found that approximately 85% of women were willing to accept a 50:50 chance of treatment failure to avoid hysterectomy.[484] [EL = 3]

A third patient preference study ($n = 221$) examined women's priorities from treatment for menorrhagia. The study found that 'stops periods for good' and 'back to usual activities as soon as possible' were the two most important wishes of women. These data show the dichotomy between women's wish to avoid hysterectomy and desire to stop menstrual periods.[245] [EL = 3]

A fourth patient preference study (23 focus groups) used qualitative methods to examine women's experiences of undergoing hysterectomy. The study found that women try to avoid hysterectomy where possible, but when they do undergo surgery they are generally satisfied.[485] [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.[486] [EL = 3]

No RCTs examining prognostic factors or indications for hysterectomy were identified. However, RCTs examining the therapeutic effect of various 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 on only consensus.

12.1.2 Evidence statements on indications for hysterectomy

Evidence from one systematic review and five observational studies was identified. The systematic review states that investigations for causes of HMB, attempts at pharmaceutical treatment and provision of full information to 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 pharmaceutical treatment and full information provision to the woman. In addition, hysterectomy is only indicated where HMB is causing anaemia and/or serious HRQoL 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 determinant of the route of the hysterectomy. However, owing to differences in the measurement of uterine size there are no definitive cut-off points for route selection.

12.1.3 GDG interpretation of evidence on indications for hysterectomy

The GDG placed a high value on women retaining their uteri, on minimising the invasiveness of surgery and on patient choice.

Recommendations on indications for hysterectomy

See Section 12.3 for recommendations.

12.2 Hysterectomy

A number of methods of hysterectomy are used by surgeons, and these are based around three main routes of surgery: abdominal hysterectomy (AH), vaginal hysterectomy (VH) and laparoscopic hysterectomy (LH). LH has three subdivisions: laparoscopically 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 (a large uterus and/or uterine fibroids make it more difficult to use the less invasive techniques), the location of any uterine fibroids, the mobility of the uterus and the size and shape of the vagina.

12.2.1 Review of hysterectomy

Overview of available evidence

Two reviews, four RCTs and one cohort study were identified comparing hysterectomy with other treatments (Figure 12.1). One review and one subsequent RCT were found on the route of hysterectomy, and three RCTs were identified on total versus sub-total hysterectomy. Further information is provided in evidence tables 12.2 and 12.3 and in Figure 12.3 at the end of this chapter.

Hysterectomy versus pharmaceutical treatment

One RCT ($n=63$) was identified that compared hysterectomy against further pharmaceutical treatment in a population of women with abnormal uterine bleeding (AUB). The rate of continued vaginal bleeding at 24 months was 37% for pharmaceutical treatment and 7% for hysterectomy ($P<0.001$), with the continued bleeding in the hysterectomy group being due to crossover between treatment arms. The hysterectomy group had a significant reduction in symptoms, except for stress urinary incontinence ($P=0.34$) and urge urinary incontinence ($P=0.74$). The pharmaceutical 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 pharmaceutical treatment group had undergone a

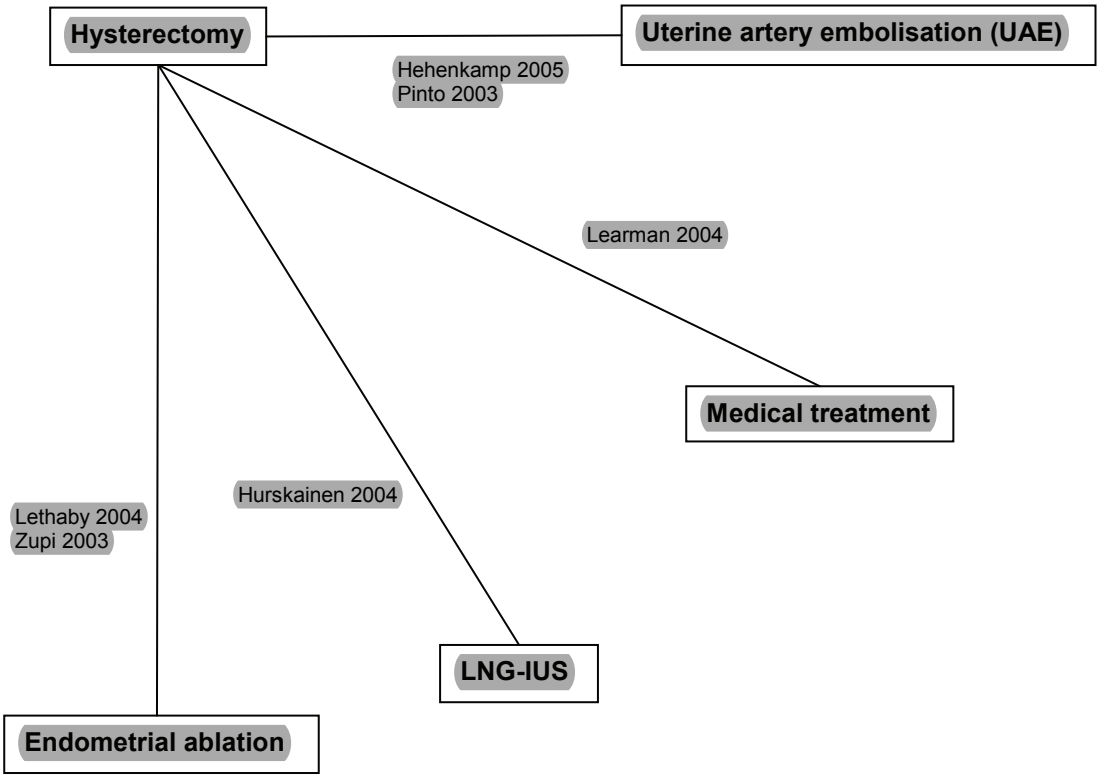

Figure 12.1 RCT evidence base for comparisons between hysterectomy and other treatments[104,119,333,335,418,420]

hysterectomy. The results suggest that after failed pharmaceutical treatment a hysterectomy produces better outcomes for women than further pharmaceutical treatment. However, the results also show that some women do benefit from further pharmaceutical treatment and do not require a hysterectomy.[119,326] [EL = 1+]

Hysterectomy versus LNG-IUS

One RCT ($n = 236$) was identified comparing hysterectomy with LNG-IUS for the treatment of HMB. The HRQoL 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.[105] The 5 years follow-up showed no difference between interventions, in terms of HRQoL. However, a large proportion of the LNG-IUS group had undergone hysterectomy by 5 years.[104] [EL = 1++]

In a separate analysis of different subgroups ($n = 236$), neither the 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 menorrhagia (> 80 ml MBL) showed that in the LNG-IUS group women without menorrhagia had better HRQoL outcomes than women with menorrhagia for anxiety ($P = 0.04$) and EQ-5D ($P = 0.05$). In the hysterectomy group, women without menorrhagia had better outcomes than those with menorrhagia for anxiety ($P = 0.007$), emotional wellbeing ($P = 0.01$) and energy ($P = 0.0002$). Women with menorrhagia had better outcomes with hysterectomy than LNG-IUS for anxiety ($P = 0.003$), general health ($P = 0.04$), energy ($P = 0.05$) and pain relief ($P = 0.04$). Furthermore, multiple regression analysis showed that MBL was the most significant factor predicting outcome.[483] [EL = 2−]

Hysterectomy versus endometrial ablation

One systematic review (five RCTs) was identified that compared hysterectomy with endometrial ablation. The review found that, in terms of reduction in MBL, hysterectomy provided greater reductions (at 12 months (three studies, $n = 440$) OR 0.12 [95% CI 0.06 to 0.25]). Patient satisfaction also favoured hysterectomy (at 12 months (three studies, $n = 519$) OR 0.46 [95% CI 0.24 to 0.88]; at 24 months (three studies, $n = 354$) OR 0.31 [95% CI 0.16 to 0.59]). However, 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 ($P = 0.007$), which were all in favour of hysterectomy. Endometrial ablation techniques required less time to undertake, shorter hospital stays and had fewer adverse events (duration of procedure (five studies, $n = 706$) WMD = −23.1 minutes [95% CI −23.8 to −22.3] in favour of ablation/resection; duration of hospital stay (five studies, $n = 706$) WMD = −4.91 days [95% CI −4.95 to −4.87] in favour of ablation/resection; 13 types of adverse event were reported and the results favour 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 7.33 [95% CI 4.18 to 12.86]). The review concluded that ablation/resection is an alternative to hysterectomy, but is less effective at reducing MBL and improving satisfaction. However, ablation/resection does lead to shorter duration of surgery and fewer complications.[330] [EL = 1++]

One subsequent RCT ($n = 203$) compared transcervical resection of the endometrium (TCRE) with laparoscopic hysterectomy. The study found that hysterectomy took longer (operating times: TCRE = 41.7 minutes, LH = 71.5 minutes, $P < 0.01$), there was no difference in complications and by 2 years follow up a higher proportion of the TCRE group required additional surgery (TCRE = 12, LH = 1). For HRQoL outcomes (SF-36), there were significant improvements from baseline scores for general health and social functioning, and for hysterectomy only in emotional role and vitality. Furthermore, there were significant differences between the groups in favour of hysterectomy for general health, social function and vitality scores ($P < 0.01$).[333] [EL = 1+]

A subgroup analysis ($n = 204$) of an RCT already reported found no difference in ovarian or bladder function between ablation and hysterectomy groups.[360] [EL = 2+]

A cohort study comparing hysterectomy and ablation (TCRE $n = 3845$, hysterectomy $n = 3397$, hysterectomy and bilateral salpingo-oophorectomy (BSO) $n = 2305$) reported 5 year follow-up results and found a higher loss of libido among women who had undergone hysterectomy or

BSO (loss of libido for hysterectomy compared with TCRE OR 1.42 [95% CI 1.22 to 1.65], and for hysterectomy and BSO compared with TCRE OR 1.80 [95% CI 1.51 to 2.14], $P<0.001$), the same for loss of sexual arousal but not for vaginal dryness. The study concluded that, at 5 years follow-up, women who had undergone hysterectomy reported an increase in psychosexual problems compared with those who had undergone TCRE, and these figures were higher for women who had had BSO at the time of hysterectomy.[380] [EL = 2++]

A subsequent publication based on the same cohort ($n=11\,323$) showed that women undergoing hysterectomy have higher OR of developing urinary symptoms than women having TCRE, 5 years after surgery. Furthermore, the study shows that women undergoing LAVH have higher OR of developing urinary symptoms than those undergoing vaginal or abdominal hysterectomy.[381] [EL = 2+]

UAE versus hysterectomy

One review was identified (three RCTs) comparing UAE with hysterectomy or myomectomy. The review identified RCT evidence on UAE.[416] [EL = 1+] One subsequent RCT has been published.

For the RCT studies comparing UAE with hysterectomy, the review reported a shorter duration of procedure (WMD −16.4 minutes [95% CI −26.0 to −6.8]), less intra-procedure blood loss (WMD −405 ml [95% CI −513 to −298]), shorter length of hospital stay (WMD −3.27 days [95% CI −3.77 to −2.77]) and quicker resumption to normal activities (WMD −26.7 days [95% CI −36.2 to −17.2]) 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]) or 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]).

Comparison of the various routes of hysterectomy

One systematic review (27 RCTs, $n=3643$) assessed the most appropriate surgical approach to hysterectomy for women with benign gynaecological conditions.[487] [EL = 1++]

The review reported that the operation time for AH was significantly shorter than that for LH (WMD 10.6 minutes [95% CI 7.4 to 13.8]), statistical heterogeneity was present for the operation time for LH versus AH ($P=0.00001$), and that VH had a significantly shorter operation time than LH (WMD 41.5 minutes [95% CI 33.7 to 49.4]). No results for AH versus VH were presented.

The review assessed complication rates associated with the various routes (see Tables 12.1 and 12.2). Where bladder and ureter injuries were pooled as 'urinary tract injury', there was a significant increase for LH versus AH (OR 2.61 [95% CI 1.22 to 5.60]), but there were no statistically significant differences for LH versus VH (OR 1.00 [95% CI 0.36 to 2.75]) or for LH(a) versus LAVH (OR 1.60 [95% CI 0.29 to 7.83]). There were significantly fewer wound or abdominal wall infections (OR 0.32 [95% CI 0.12 to 0.85]) and significantly fewer unspecified infections or occurrence of pyrexial illness (OR 0.65 [95% CI 0.49 to 0.87]) for LH versus AH. There were significantly fewer unspecified infections/febrile episodes in VH compared with AH (OR 0.42 [95% CI 0.21 to 0.83]). Hospital stay was shorter (WMD 1.0 days [95% CI 0.7 to 1.2) and return to normal activities quicker (WMD 9.5 days [95% CI 6.4 to 12.6]) in women undergoing VH when compared with AH.

Recovery time was also shorter in LH compared with AH (hospital stay WMD 2.0 days [95% CI 1.9 to 2.2]; return to normal activities WMD 13.6 days [95% CI 11.8 to 15.4]).[487] There were no significant differences in recovery time from surgery, in terms of hospital stay or return to normal activities, for LH versus VH, or in terms of hospital stay for LH(a) versus LAVH.

The study concluded that 'when technically feasible, VH should be performed in preference to AH because of more rapid recovery and fewer febrile episodes postoperatively. Where VH is not possible, LH has some advantages over AH (including less operative blood loss, more rapid recovery, fewer febrile episodes and wound or abdominal wall infections) but these are offset by longer operating time and more urinary tract (bladder or ureter) injuries. No advantages of LH over VH could be found and LH operations took longer… The surgical approach to hysterectomy

should be decided by a woman in discussion with her surgeon in light of the relative benefits and hazards'.

However, the majority of the evidence for hysterectomy is based on mixed populations and therefore any results have to be extrapolated to an HMB-specific population. In addition, the systematic review did not assess whether the groups included in the RCTs were balanced at baseline. Analysis of baseline characteristics (see Figure 12.2) showed that, on average, women in less invasive groups had a smaller uterine size than those in the more invasive groups (the plot is based on means and medians and thus no statistical analysis could be performed to assess the significance of the differences in average uterus size). While 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.

Furthermore, the issue of surgeon training and experience was not taken into account in the review, and many of the studies included in the review were undertaken to demonstrate that LH surgery could be performed 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 of LH techniques against VH and AH methods. This may mean an overemphasis in the evidence base on LH techniques.

Details of the RCTs included in the review can be found in evidence table 12.2.[488–515]

A subsequent publication ($n = 74$), based on an RCT comparing LH with AH already included in the review, examined psychological wellbeing and found that both groups improved from baseline on a number of components, but neither on total score (baseline: 93.9 [SD 23.7] versus 92.0 [SD 18.7]; 1 year: 102.8 [SD 15.8] versus 97.3 [SD 19.1]). There were no differences between the groups on psychological or psychosexual scores. This study implied that psychological wellbeing and sexuality after hysterectomy are not influenced by surgical technique. The numbers included in the study are different between the two publications, and 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 with AH, and these were reported in several publications (not all included in this review).[492] [EL = 1+]

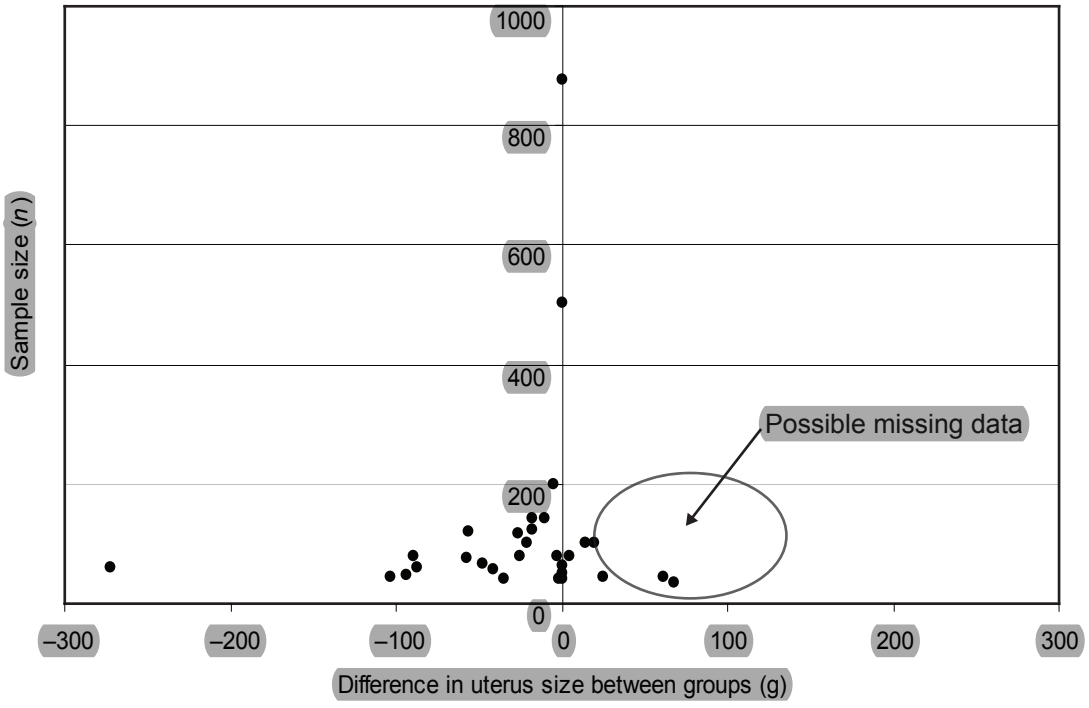

Figure 12.2 Bias in hysterectomy trials; difference in average uterus size between groups within RCTs comparing different types of hysterectomy (least invasive option minus most invasive option)

One subsequent RCT ($n=30$) on women (15 AH, 15 VH) compared AH with VH in women with benign gynaecological conditions. Duration of operation favoured AH (69.1 minutes versus 85.3 minutes, $P<0.0001$) whereas length of stay (7.2 days versus 3.1 days, $P<0.0001$) and tissue damage markers favoured VH. The study concluded that the methods were equivalent.[516] [EL = 1–]

Hysterectomy in the 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'.[517] [EL = 1+]

Total versus sub-total hysterectomy

Three RCTs comparing total versus sub-total hysterectomy were identified. An RCT ($n=319$) compared total hysterectomy with sub-total hysterectomy to treat benign gynaecological conditions. At 12 months follow-up, the study found a statistically significant difference between groups for urinary incontinence (13 versus 24, OR 2.08 [95% CI 1.01 to 4.29], $P=0.043$) in favour of total hysterectomy. However, there were no statistically significant differences between groups for quality of life (measured on SF-36), constipation, prolapse, satisfaction with sex life, pelvic pain, vaginal bleeding or complication rates.[518] [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 versus 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) showing no statistically significant differences at 12 months. 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 211.0], $P=0.001$) and incomplete bladder emptying (OR 20.0 [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.[519]

An RCT compared bladder, bowel and sexual functions and postoperative outcomes between women undergoing sub-total hysterectomy ($n=133$) and total hysterectomy ($n=146$). It reported a significant reduction in urinary frequency (more than seven times a day) in both groups at 12 months (33% in sub-total hysterectomy and 31% in total hysterectomy before surgery versus 24% and 20%, respectively, after surgery). The reduction in nocturia and stress incontinence and the improvement in bladder capacity were also similar in both groups. There were no significant changes in bowel functions or sexual function in either group after surgery. Hospital stay was significantly shorter in the sub-total hysterectomy group (5.2 days versus 6 days; difference −0.8 days [95% CI −1.6 to −0.04]). The rate of post-surgery fever was significantly lower in the sub-total hysterectomy group (6% versus 19%). After sub-total hysterectomy, 7% of women had cyclical bleeding and 2% had cervical prolapse.[520] [EL = 1+]

One RCT compared surgical complications and clinical outcomes of women undergoing total abdominal hysterectomy ($n=67$) versus supra-cervical hysterectomy ($n=68$) for AUB due to benign causes. There was a significant reduction in symptoms such as pelvic pain or pressure, back pain, urinary incontinence and voiding dysfunction. There were no significant differences between the two groups in the rates of complications, degree of symptom improvement, hospital readmission or activity limitation. There was a significant association between baseline body weight of >100 kg and hospital readmission (RR 2.18 [95% CI 1.06 to 4.48]).[499] [EL = 1+]

The same RCT also assessed sexual functioning after surgery and reported a similar improvement in both groups during the first 6 months after surgery, but it had stabilised by 1 year. There was no significant difference in the mean score on the Sexual Function Scale between the two groups (82 in the supra-cervical hysterectomy group versus 80 in the total abdominal hysterectomy group on

a 0–100 scale with 100 indicating an absence of problems; difference +2 [95% CI −8 to +11]) at 2 years.[521] [EL = 1+]

These results indicate that complications and adverse events are similar with total and sub-total hysterectomy. Therefore, the decision about which method to use should be based on other criteria.

Observational studies

Given the availability of RCT evidence on hysterectomy, the need to examine observational studies is reduced. However, what observational studies provide is long-term outcome data, which is especially important where major surgery is undertaken, and it is for this reason that they are included. A summary of the complication rates for the various types of hysterectomy, as reported by the observational and RCT studies, is shown in Tables 12.1 and 12.2, respectively.

Table 12.1 Hysterectomy complication rates reported by long-term cohort studies

Complication	Abdominal hysterectomy	Vaginal hysterectomy	Laparoscopically assisted vaginal hysterectomy, laparoscopic hysterectomy or total laparoscopic hysterectomy
Death	0.38 per 1000 (0.25 to 0.64) within 6 weeks. RR 0.82 (0.73 to 0.93) within 5 years		
Major operative complications (%)	3.6	3.1	6.1
Major postoperative 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 (OR)	1.51 (1.20 to 1.90)	1.15 (0.96 to 1.37)	1.33 (0.85 to 2.07)
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)

ORs calculated against general population. All ranges are 95% confidence intervals.

Table 12.2 Hysterectomy complication rates reported in RCTs included in the Cochrane review[487]

Complication	Abdominal hysterectomy	Vaginal hysterectomy	Laparoscopically assisted vaginal hysterectomy, laparoscopic hysterectomy or 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 haematoma (%)	6.00	4.04	3.94
Vaginal cuff infection (%)	2.06	1.93	4.15
Wound abdominal wall infection (%)	7.38	0.00	1.92
Laparotomy (%)	—	2.66	4.17
Urinary tract injury (bladder or urethral) (%)	0.86	1.60	2.33
Bleeding (%)	1.57	0.00	0.37
Urinary tract infection (%)	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

A UK case series ($n=37\,295$ cases of hysterectomy) reported that complications occurred perioperatively and postoperatively in 3% and 1%, respectively, of women undergoing hysterectomy. Hysterectomy for fibroids was associated with significantly more complications than women with DUB (adjusted OR 1.34 [95% CI 1.14 to 1.56]). LAVH doubled the risk of operative complications compared with AH (adjusted OR 1.92 [95% CI 1.48 to 2.50]). Both VH and LAVH techniques had a significantly higher risk of complications than AH (adjusted OR 1.39 [95% CI 1.01 to 1.90] and adjusted OR 1.64 [95% CI 1.00 to 2.68], respectively). A reduction of risk was associated with increasing age in women undergoing hysterectomy for fibroids, but not DUB. Fourteen deaths were reported within the 6 week period following surgery.[522,523] This study represents the best available evidence on complication rates for hysterectomy within the UK. Only 45% of hysterectomies were reported to this study. Analysis of a proportion of women not reported to the study suggests a three-fold higher rate of complications.[380] [EL= 3]

A retrospective review of medical records of women undergoing hysterectomy ($n=1940$) for benign and non-obstetric indications, over a 10 year period, reported an overall mortality rate of 1.5 per 1000 women. The overall complication rates were 44% for AH and 27.3% for VH, and unintended major surgical procedures were required in 3% and 1% of AH and VH, respectively. The AH group was four times more likely than the VH group to require surgical intervention (36% versus 9%) at readmission. VH was associated with a lower febrile morbidity and minor complication rate. Prophylactic antibiotics significantly reduced the febrile morbidity by 50% and 40% of VH and AH, respectively.[524] [EL= 3]

A review of hysterectomy studies ($n=3112$ LAVH, $n=1618$ total abdominal hysterectomy, $n=690$ VH, from 34 studies) examined the reported complication rates. The review reported higher complication rates for LAVH compared with total abdominal hysterectomy for bladder, ureter and bowel trauma, fistula, and pulmonary embolus, but lower rates of sepsis and transfusion. However, the review highlighted that differences in data collection between studies could impact on results.[525] [EL = 3]

A case note review of women undergoing hysterectomy ($n=1299$) reported significant reductions in symptom severity (vaginal bleeding, pelvic pain, back pain, activity limitation, sleep disturbance, fatigue, abdominal bloating, urinary incontinence) and significant improvements in psychological function and quality of life at 2 years after hysterectomy. There was a significant association between lack of symptom relief and being in therapy for depression at the time of hysterectomy (OR 3.45 [95% CI 1.84 to 6.51]) and having a low income (OR 0.37 [95% CI 0.24 to 0.59]) at 2 years. Women who had bilateral oophorectomy at the time of hysterectomy were significantly more likely to report symptom relief at 2 years (OR 2.01 [95%CI 1.14 to 3.53]), but not at 1 year after hysterectomy.[526] [EL = 3]

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 gave 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 was 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 concluded that, at a maximum willingness-to-pay per QALY of £30,000, the probability that laparoscopic hysterectomy is cost-effective compared with abdominal hysterectomy is 56%.[527]

One study ($n=200$) compared laparoscopic hysterectomy with abdominal hysterectomy only.[500] This study found that the length of time required for laparoscopic hysterectomy procedures was longer than for abdominal hysterectomy (81 minutes [SD 30] versus 47 minutes [SD 16], $P<0.001$). Laparoscopic hysterectomy was associated with shorter hospital stay (4 days versus 6 days). There were no differences between the rate of recovery and patient satisfaction of either treatment. Laparoscopic hysterectomy cost more on average than abdominal hysterectomy (£2,112 versus £1,667). Because no differences were reported in EQ-5D analogue scale

scores, an incremental cost-effectiveness ratio was not calculated. The study concluded that because there were no differences in clinical outcomes, patient-reported outcomes or patient-reported quality of life, laparoscopic hysterectomy is unlikely to be cost-effective compared with abdominal hysterectomy.

One study ($n=80$) compared laparoscopic hysterectomy and abdominal hysterectomy where bilateral salpingo-oophorectomy was indicated in all participants. This study found that laparoscopic vaginal hysterectomy (£1,260) was less costly than abdominal hysterectomy (£1,750). Confidence intervals for the costs were not presented. Laparoscopic vaginal hysterectomy took longer to perform than abdominal hysterectomy (100 minutes [SD 5.6] versus 57 minutes [SD 4.7], $P<0.0001$). However, women who underwent laparoscopic hysterectomy had shorter length of stay in hospital (3.5 days versus 6 days, $P<0.0001$), quicker recovery from pain (13 days versus 26 days, $P<0.0001$) and quicker return to work (21 days versus 42 days, $P<0.0001$). Although laparoscopic surgery is more costly to perform, the difference in total cost between methods is explained by earlier discharge from hospital. Additional benefits may accrue to the woman through quicker postoperative recovery and return to work.[506]

12.2.2 Evidence statements for hysterectomy

Evidence from one systematic review, five RCTs and five observational studies comparing hysterectomy with 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 (three studies, $n=519$) OR 0.46 [95% CI 0.24 to 0.88], and at 24 months (three studies, $n=354$) OR 0.31 [95% CI 0.16 to 0.59]).

Evidence from one systematic review of RCTs, one subsequent RCT and four large non-comparative studies compared the various routes of hysterectomy. The data suggested 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 days [95% CI 0.7 to 1.2] and return to normal activities WMD 9.5 days [95% CI 6.4 to 12.6]), and that 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 uterine mobility are all contra-indications to the vaginal route being used.

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 who were indicated for bilateral salpingo-oophorectomy found laparoscopic hysterectomy to be less costly than abdominal hysterectomy. One study was of high quality and measured outcomes in QALYs. In this study, the size of the difference between the costs was large in comparison with the difference in outcomes measured in QALYs. Laparoscopic hysterectomy is not likely to be cost-effective when compared with vaginal hysterectomy at any level of willingness-to-pay per QALY. When compared with abdominal hysterectomy, laparoscopic hysterectomy is unlikely to be cost-effective below the threshold of £20,000 per QALY. No direct cost-effectiveness comparisons were made between vaginal and abdominal hysterectomy.

Hysterectomy undertaken for uterine fibroids was associated with significantly more post-operative complications than when performed for DUB (adjusted OR 1.46 [95% CI 1.10 to 1.95]). Evidence from three RCTs showed that where abdominal hysterectomy was indicated, sub-total hysterectomy was associated with higher rates of urinary incontinence than total hysterectomy, but had quicker recovery times than total hysterectomy, and was equivalent to total hysterectomy on all other measures. Further information is provided in evidence tables 12.1 to 12.3.

12.3 Pre-treatment for hysterectomy

Pre-treatment before hysterectomy is often recommended in situations where uterine fibroids are present. The rationale is that pre-treatments, such as GnRH-a, reduce the size of fibroids, make surgery easier and even allow for the less invasive vaginal route to be used.

12.3.1 Review of pre-treatment for HMB

One systematic review (26 RCTs) was found that assessed 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 to 18 gestational weeks, or fewer than four myomas larger than 4 cm in diameter, or myomas less than 10 cm in diameter, or fibroid size/volume up to 238 ml).[469] [EL = 1+]

Pre- and postoperative haemoglobin and haematocrit were significantly improved by GnRH-a 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 with GnRH-a therapy. Hysterectomy appeared to be easier after pre-treatment with GnRH-a: operating time was reduced 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-a for 3–4 months prior to fibroid surgery reduces both uterine volume and fibroid size. However, this review included both hysterectomy and myomectomy studies, and examined uterine fibroids rather than HMB. Therefore, the results of this review can only be applied to women with HMB in the presence of uterine fibroids.

An RCT ($n = 188$), which was excluded from review, compared nafarelin nasal spray with placebo in women with uterine fibroids scheduled for hysterectomy. The study found that at 3 months the uterus size in the nafarelin group was on average 23.7% smaller and in the placebo group 14.2% larger ($P < 0.001$ from baseline, $P < 0.05$ between groups). However, adverse events were higher in the nafarelin group (107 versus 59).[528] [EL = 1–]

A subsequent RCT ($n = 51$) was identified comparing leuprorelin with a control group for hysterectomy in women with DUB. The study found no statistical differences between groups for operative issues, complications or patient outcomes, probably owing to the small sample size.[529] [EL = 1–]

GDG interpretation of evidence on hysterectomy

The GDG placed a high value on avoiding surgery and minimising the severity of surgery.

Owing to the fact that hysterectomy stops any further menstrual bleeding, the GDG focused on HRQoL 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:

- The populations in the studies included any benign gynaecological condition and therefore were not directly applicable to HMB.
- Evidence was found of a systemic bias towards smaller uterine size in test groups, compared with control groups. This may result in an overestimation of any benefits of test interventions.
- The evidence base was skewed towards investigation of laparoscopic hysterectomy, suggesting a bias among researchers towards investigation of this technique.
- 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.

The GDG interpretation of the available evidence thus took these issues into account when making recommendations.

Recommendations on hysterectomy

Hysterectomy should not be used as a first-line treatment solely for HMB. Hysterectomy should be considered only when:

- other treatment options have failed, are contraindicated or are declined by the woman
- there is a wish for amenorrhoea

- the woman (who has been fully informed) requests it
- the woman no longer wishes to retain her uterus and fertility. [C]

Women offered hysterectomy should have a full discussion of the implication of the surgery before a decision is made. The discussion should include: sexual feelings, fertility impact, bladder function, need for further treatment, treatment complications, the woman's expectations, alternative surgery and psychological impact. [D(GPP)]

Women offered hysterectomy should be informed about the increased risk of serious complications (such as intraoperative haemorrhage or damage to other abdominal organs) associated with hysterectomy when uterine fibroids are present. [C]

Women should be informed about the risk of possible loss of ovarian function and its consequences, even if their ovaries are retained during hysterectomy. [D(GPP)]

Individual assessment is essential when deciding the route of hysterectomy. The following factors need to be taken into account:

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

Taking into account the need for individual assessment, the route of hysterectomy should be considered in the following order: first line vaginal; second line abdominal. [A]

Under circumstances such as morbid obesity or the need for oophorectomy during vaginal hysterectomy, the laparoscopic approach should be considered, and appropriate expertise sought. [D(GPP)]

When abdominal hysterectomy is decided upon then both the total method (removal of the uterus and the cervix) and subtotal method (removal of the uterus and preservation of the cervix) should be discussed with the woman. D[(GPP)]

Research recommendations for hysterectomy

- An investigation into the medium- and long-term outcomes of sub-total and total hysterectomy.
- An investigation into the effect of hysterectomy and oophorectomy on cancer.

Implementation advice for hysterectomy

Commissioners of health care should offer all types of hysterectomy to women in order to allow choice. This requires that surgeons with the training and experience to undertake each type of surgery be accessible. Given that the number of hysterectomies performed for menstrual disorders has more than halved in the past 10 years, consideration should be given to specialist training in hysterectomy for HMB.

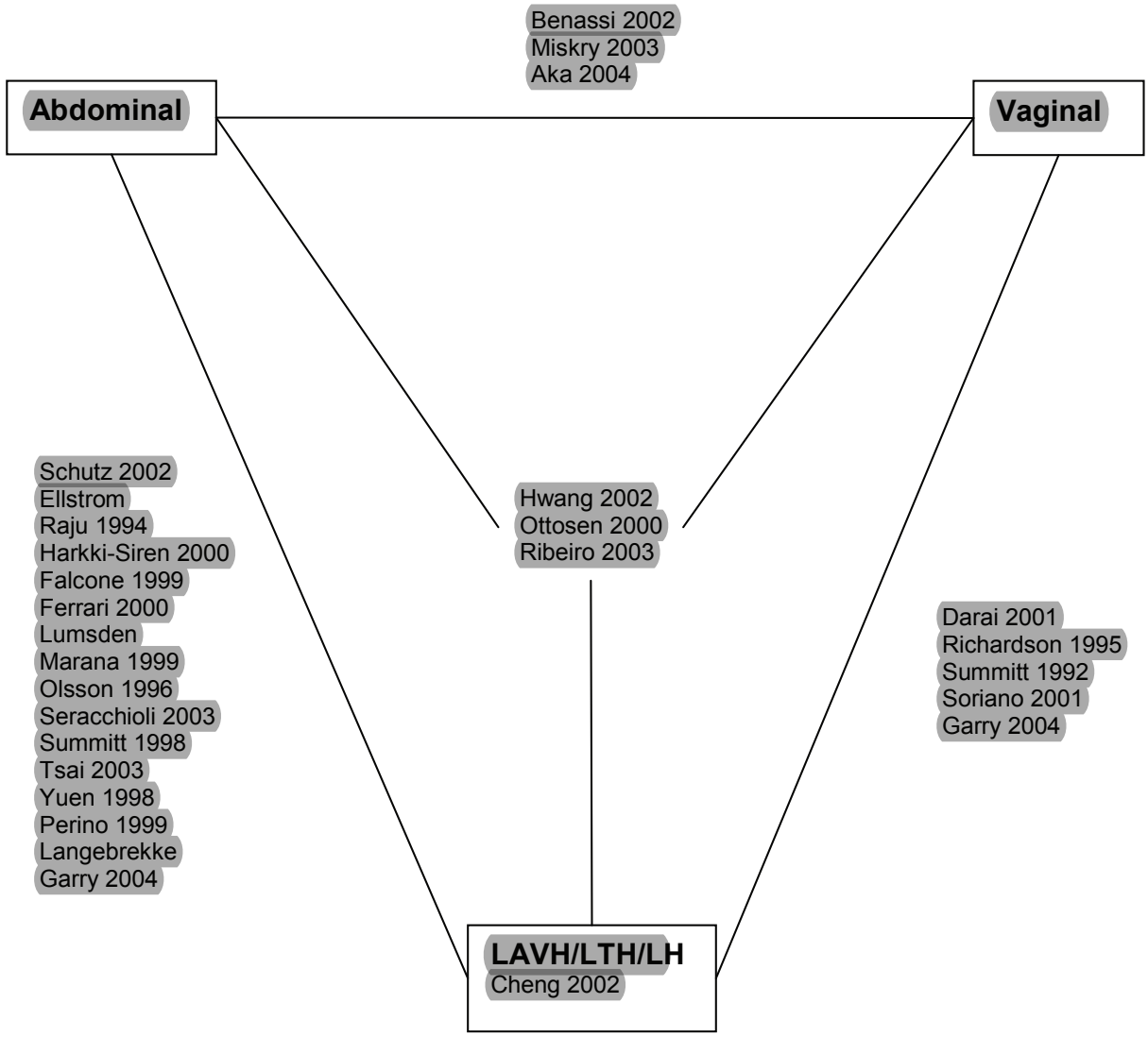

Figure 12.3 Evidence base for comparisons of route of hysterectomy[488,489,492–494,496–498,500–514,516,517,527,530]

13 Removal of ovaries at the 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.

13.1 Oophorectomy

13.1.1 Oophorectomy and HMB

No studies were identified linking HMB and the need for oophorectomy.

13.1.2 Prophylactic oophorectomy for prevention of cancer

A number of studies were identified relating to the prophylactic use of oophorectomy for prevention of cancer. Further information is provided in evidence tables 13.1 and 13.2.

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). Information on this is published elsewhere.[531–538] Women with genetic *BRCA1* or *BRCA2* mutations are at greater risk of ovarian and breast cancer.[539,540] [EL = 3; EL = 3]

Retrospective studies looking at prophylactic oophorectomy at the time of vaginal hysterectomy have shown that the ovaries can be removed successfully in 65–97% of patients.[541,542] [EL = 2−; EL = 2+] One case series found no significant increase in operating time, estimated blood loss, length of hospital stay or postoperative morbidity between women who had their ovaries removed and those who did not.[541] [EL = 2−] Another case series found that oophorectomy added 23.4 minutes to the total operating time compared with vaginal hysterectomy alone.[542] [EL = 2+]

A retrospective case–control study investigated women who had chosen prophylactic oophorectomy at the time of hysterectomy instead of prolonged screening and suggested that these women may have more physical and emotional symptoms than women who remain on an ovarian cancer screening programme, but that they report equivalent levels of cancer worry.[253] [EL = 3]

A qualitative study ($n = 16$) found that women who want to retain their ovaries had diametrically opposite opinions to those women who wanted oophorectomy. Women who wanted to retain ovaries viewed them as a healthy organ that did not need removing, while women who wanted oophorectomy viewed ovaries as a source of problems and needing to be removed.[543] [EL = 3]

Women and clinicians considering prophylactic oophorectomy at the time of hysterectomy should consider the use of other treatments, continued 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.

13.1.3 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 ovarian cancer. Further information is provided in evidence tables 13.1 and 13.2.

13.1.4 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 subsequently to hysterectomy can present technical problems for the surgeon
- not undertaking oophorectomy at the 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 because of HRQoL issues such as long-term HRT use and loss of fertility
- the likelihood of residual ovary syndrome occurring has to be considered as an indication for oophorectomy
- in the past, ovaries have been removed without obvious reason.

Recommendations on oophorectomy

Removal of healthy ovaries at the time of hysterectomy should not be undertaken. [D(GPP)]

Removal of ovaries should only be undertaken with the express wish and consent of the woman. [D(GPP)]

Women with a significant family history of breast or ovarian cancer should be referred for genetic counselling prior to a decision about oophorectomy.* [D(GPP)]

In women under 45 considering hysterectomy for HMB with other symptoms that may be related to ovarian dysfunction (for example, premenstrual syndrome), a trial of pharmaceutical ovarian suppression for at least 3 months should be used as a guide to the need for oophorectomy. [D(GPP)]

If removal of ovaries is being considered, the impact of this on the woman's wellbeing and, for example, the possible need for hormone replacement therapy (HRT) should be discussed. [D(GPP)]

Women considering bilateral oophorectomy should be informed about the impact of this treatment on the risk of ovarian and breast cancer. [D(GPP)]

* See 'The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care', NICE clinical guideline 41, www.nice.org.uk/CG041, for more detail.

14 Competencies

Introduction

Many of the interventions and diagnostic tools examined in this guideline require a high degree of operator competence. In this chapter, the minimum training and education requirements are outlined for an operator to be considered competent to undertake the following procedures:

- ultrasound
- fitting 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.

14.1 Competencies

14.1.1 Review on competencies

Limited data was identified from literature searches on issues relating to competencies. Further information is provided in evidence tables 14.1 and 14.2. 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. However, reference should be made to the NICE *Long-acting Reversible Contraception* (LARC) guideline on the competencies needed to fit an LNG-IUS.[286]

Endometrial ablation

One audit study on endometrial ablation found that of 5388 TCRE procedures undertaken, 1095 were by surgeons who had not attended a training course and who were not supervised. The study also found that of 983 laser ablations undertaken, 15 were by surgeons who had not attended a training course and who were not supervised. The study did not assess the outcomes of surgery, so it is not known what effect the lack of training or supervision had.[544] [EL = 3]

An audit undertaken in the UK examined 18 641 endometrial ablations. The study found a statistically significant trend in rates of immediate complications assessed by operator volume ($P < 0.05$).[545] [EL = 3]

An audit undertaken in Scotland examined 978 endometrial ablations. The audit found no association between operator volume and complication or satisfaction rates. However, the audit was based on voluntary submission of results.[546] [EL = 3]

Myomectomy

No references were found for this procedure.

UAE

One set of training standards for UAE specified that training fellows must undertake 100 arteriographic procedures, including at least 50 visceral artery catheterisations and 25 selective embolisation procedures per year.[547] [EL = 4]

One set of training standards for UAE specified that training fellows must undertake 50–150 diagnostic arteriograms, 65–130 angioplasties and an unspecified number of visceral artery embolisations.[548] [EL = 4]

One article on volume–outcome relationships was identified. This suggested that between 12.5 and 25 UAEs need to be undertaken per year to remain competent.[549] [EL = 4]

Hysterectomy and 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.[550] [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.[551] [EL = 2+]

One audit study ($n = 20\,249$) found that difference between expected and actual mortality rates for hysterectomy for any indication were related to volume of procedures performed (actual versus expected mortality by volume performed: 1–24 hysterectomies per year OR 1.874; 361 or more hysterectomies per year OR 0.733).[552] [EL = 3]

One study ($n = 6609$) found that complication rates with hysterectomy for any indication were related to volume of procedures undertaken (OR comparing low to high volume by procedure: hysterectomy = 1.35 [95% CI 1.00 to 1.82]).[553] [EL = 3]

These results do not allow a specific figure to be outlined for the minimum numbers of procedures to be performed. What they do show is that a volume–outcome relationship is likely to exist, and therefore a policy towards higher rather than lower volume of surgery by surgeons and within hospitals should be encouraged.

14.1.2 GDG discussion on competencies

Given the limited amount of evidence available on competencies, the GDG discussion was the basis for recommendations. In addition, meetings were held with experts and their views were included in the discussion. The GDG discussion highlighted the following issues:

- There is significant variability in training undertaken by clinicians. (The GDG defined a training programme as any form of formal education, such as apprenticeship or course attendance.) The GDG felt that it is essential that any operator must have completed an accredited training programme provided by a relevant professional organisation before undertaking a procedure.
- Given the limited data available on volume–outcome effects, the GDG did not feel that they could make valid recommendations on a minimum level of activity. However, they did feel that encouraging higher volume was necessary, and that this may mean limiting the number of practitioners undertaking a procedure.
- However, the GDG stated that any minimum level of activity would have to take into account the patient case-mix and the generic nature of procedures, such as the ability to close wounds.
- The GDG felt that there is a need for a service framework to be in place for maintaining competencies and audit standards. This was seen as being of major importance. Once a

framework is in place, standards outlined in guidelines could be implemented in a systematic manner. If frameworks do not exist then introduction of standards is more difficult.

- Any system should include a mechanism for the reporting of any complications to the operator and for a regular forum for discussion of cases among colleagues.
- The GDG felt that information on operator competence should be available to any prospective patient. This information could include training completed, number of procedures undertaken and their complication rates. However, the GDG recognised that providing raw figures without explanation could create confusion for women about what they meant.
- Given that the range of treatments available is increasing and the number of women being treated is stable or falling, it was felt that there was a need for subspecialty training and accreditation. For example, not all trainees may need to be trained in hysterectomy for HMB as not all will be required to undertake this procedure.
- A system needs to be in place for MHRA Device Alerts to be incorporated into training programmes.
- One option that the GDG believed would be helpful was that referral for a procedure should be to a specific operator with special interest or training in the area. This will ensure that any potential volume–outcome effect is maximised and clinical governance ensured.
- Given the range of endometrial ablation techniques available, it is essential that any individual undertakes education and training in each technique in order to gain proficiency in each.
- The GDG also felt that, where possible, ultrasound should be undertaken in a dedicated gynaecological ultrasound unit, as the specialist knowledge in such a unit provided better results.
- Diagnostic laparoscopy will be part of Core Training but all types of hysterectomy will be taught as part of Special Skills Modules, i.e. not all trainees will learn these skills.
- Hysterectomy for fibroids should be done in specialist centres with 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.
- An individual surgeon's figures should be available publicly.

14.1.3 Evidence statement on 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 to be completed prior to a procedure being performed without supervision. 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. Further information is provided in evidence tables 14.1 and 14.2.

Recommendations on competencies

Training

All those involved in undertaking surgical or radiological procedures to diagnose and treat HMB should demonstrate competence (including both technical and consultation skills) either during their training or in their subsequent practice. [D(GPP)]

The operative competence of healthcare professionals who are acquiring new skills in 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 and Training Board (PMETB), the Royal Colleges and/or the Society and College of Radiographers (SCoR). [D(GPP)]

Training programmes must be long enough to enable healthcare professionals to achieve competency in complex procedures when these are appropriate (for example, operations for fibroids that are large or in an awkward position, or using laparoscopic techniques). These training programmes will usually be located in units with a particular interest and sufficient workload to allow experience of these procedures. [D(GPP)]

Maintenance

Maintenance of surgical, imaging or radiological skills requires a robust clinical governance framework including audit of numbers, decision making, case-mix issues and outcomes of all treatments at both individual operator and organisational levels. These data should be used to demonstrate good clinical practice. [D(GPP)]

Established healthcare professionals should be able to demonstrate that their training, experience and current practice meets or exceeds the standards laid out for newly trained professionals. [D(GPP)]

Governance

If a healthcare professional lacks competence to undertake a procedure then they should refer the woman to a professional with the appropriate skill. Organisations that commission services should be responsible (through service specification based on robust audit data) for identifying and contracting professionals with appropriate skills. [D(GPP)]

Research recommendations on competencies

- Do volume–outcome relationships exist in gynaecological procedures, taking into account case-mix, hospital and surgeon factors?

Implementation advice on competencies

The GDG felt that the following are important to the implementation of the competency recommendations outlined above:

- a framework should be put in place for reporting of outcomes requiring further unexpected intervention, at local and national levels
- data should be captured from women and general practice records
- patient information leaflets or appointment letters should contain a feedback form for the woman to complete.

Appendix A

Health economics

Introduction

As part of the guideline development process a health economics component was included in each of the guideline questions. A systematic review of the literature was undertaken to identify relevant economic evidence for each question. Where evidence that met the inclusion criteria was identified, it was summarised in the appropriate section of the guideline. Where suitable evidence was identified, no modelling was conducted to address these questions. The areas where evidence was identified were information provision, LNG-IUS, endometrial ablation, UAE and hysterectomy.

The GDG, with the guidance of the health economist, identified two areas of the guideline pathway where it was felt health economics evidence was lacking and that further analysis through decision modelling was required. These two areas were investigations for HMB and pharmaceutical treatment for HMB. Decision-analytic models were developed to address these questions and the results are presented in this section. Where the answers to these questions inform particular clinical questions, a summary of results has also been presented in the appropriate section of the guideline.

The first question presented in this section is the cost-effectiveness of pharmaceutical treatments for menorrhagia in primary care. A number of articles relating to the cost-effectiveness of the LNG-IUS when compared with hysterectomy were identified. These are summarised in the appropriate section of the guideline.

The second question considered here is the cost-effectiveness of imaging techniques for the diagnosis of intrauterine pathologies on referral to secondary care.

A.1 Cost-effectiveness of first-line pharmaceutical treatments for uncomplicated HMB

A.1.1 Methods

This model addresses the cost-effectiveness of four drugs commonly used to treat HMB. No economic evidence comparing the effectiveness of the selected treatments was found, and the GDG considered the development of an economic model a priority, given the common nature of the problem, the high decrement to quality of life for women with the problem, and the variety of treatments commonly used. An economic model allows for the evaluation of various treatment strategies in order to compare their relative costs and benefits.

A state-transition (Markov) model was used to assess the cost-effectiveness of the four pharmaceutical treatments. Markov models used in decision analysis comprise a series of cycles of equal length. A hypothetical cohort of patients in the model spends each cycle in the model in a particular health state (e.g. good health, poor health, death). Patients can move between health states with given probabilities estimated from clinical data on the effectiveness of treatment. Each health state accrues both costs (of treatment) and health benefits associated with being in that state, measured in quality-adjusted life years (QALYs). This approach is useful because it allows for comparison of the costs and effects of alternative treatments for illnesses where disease states recur over time. This approach is therefore appropriate for HMB given the long-term nature of the condition, the very high likelihood of recurrence if treatment is stopped, and the high rates of discontinuation for some pharmaceutical treatments. The health states used in this menorrhagia

model are described in Table A.1. A 5 year time horizon was chosen as this is the maximum time for which one of the treatments considered is licensed. A 3 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 (four cycles per year).

The four treatments compared in the model are:

- combined oral contraceptive (COC) pill
- tranexamic acid
- levonorgestrel-releasing intrauterine system (LNG-IUS)
- nonsteroidal anti-inflammatory drugs (NSAIDs) – mefenamic acid.

Three distinct analyses are undertaken using the Markov model:

- all pharmaceutical treatments are compared with watchful waiting
- hormonal treatments only are compared with surgical treatment
- non-hormonal treatments only are compared with watchful waiting.

All pharmaceutical treatments versus watchful waiting

None of the four treatments can be considered the primary pharmaceutical 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 pharmaceutical treatment. This has been selected as the comparator for three reasons:

- the condition is not life-threatening and thus no treatment is a viable management option
- there is no primary medical therapy; a number of different treatments are currently licensed and prescribed for this condition
- as per the evidence presented in the guideline, there are no indications for direct referral for surgery as a first-line treatment where uncomplicated menorrhagia is suspected ('uncomplicated' here means that pathology has not been identified or is not sufficient to require specialist treatment).

Hormonal treatments versus surgical intervention

Although surgical interventions (hysterectomy and endometrial ablation) for uncomplicated menorrhagia are not considered as a comparator in the overall analysis, they play an important role in the management of this condition. In women who have completed their families and who do not wish to retain their fertility, surgical treatment may be an appropriate intervention. For this reason, a separate analysis is undertaken of those pharmaceutical treatments that provide contraceptive benefits in comparison with a direct referral to surgery.

Non-hormonal treatments versus watchful waiting

Some women may wish to retain their fertility, and a further analysis is undertaken only of those treatments that do not provide contraception (tranexamic acid and NSAIDs). These are compared with a strategy of no treatment, as surgical treatment for uncomplicated menorrhagia does not allow a woman to retain her fertility (except for myomectomy for treatment of uterine fibroids).

Structure of the model

At the beginning of each model cycle, a patient may be in one of seven specified health states. A person can only be in one health state during one cycle. Patients only move between states at the end of each cycle. All health states and probabilities used in the model are outlined in Table A.1.

Patients are assumed to enter the model at 42 years of age. It is recognised that, in practice, patients undergoing an initial pharmaceutical treatment are likely to be younger on average than those who are referred for surgery. However, there is no evidence that age has any impact on the effectiveness of pharmaceutical treatments. The model considers a hypothetical cohort of 1000 patients receiving each treatment option.

Initially the model only allows for one pharmaceutical treatment to be used before a patient is referred for surgical treatment, as no evidence was identified assessing the effectiveness of one or more subsequent treatments when the initial treatment has failed. A separate sensitivity analysis

Table A.1 Markov model health states

Health 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 state described below.
Well following pharmaceutical treatment	A patient can only enter this state following successful pharmaceutical treatment in the initial cycle. A patient in this state has no perceived heavy bleeding. It is assumed that a pharmaceutical treatment that is effective following the initial treatment cycle will continue to be effective. Patients who choose to discontinue treatment when in the 'well following pharmaceutical treatment' state are assumed to do so for reasons unrelated to the efficacy of the treatment, such as unpleasant adverse effects. Following a period spent in the 'well following pharmaceutical treatment' state, a patient may continue in this state or, for 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 pharmaceutical 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 end of the model period.
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 who 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.

has been undertaken to estimate in what proportion of women where the initial pharmaceutical treatment has failed a second pharmaceutical treatment would be cost-effective.

A.1.2 Treatment effectiveness

A systematic review of the clinical and economic evidence was conducted for the pharmaceutical treatment of HMB and is presented in Chapter 8. Wherever possible, the values used to populate the Markov model have been taken from the studies included in that review. In those instances where data was not available from the systematic review, estimates were taken from the best available published evidence source. Where no published evidence was available, the expert opinion of the GDG members was sought. The values used to estimate the clinical effectiveness for each pharmaceutical treatment are shown in Table A.2.

The complaint of HMB is a subjective one. Many women feel they have HMB yet have a monthly blood loss below the clinical cut-off point of 80 ml per cycle.[133] These women still seek treatment because of the impact of the condition on their quality of life. It is appropriate then to consider the success of any treatment for menorrhagia in terms of the women's perception of its impact on their usual blood loss, and not on the average reduction in blood loss following treatment as measured in many studies. As such, the analysis presented here considers treatment success in terms of the proportion of women who are satisfied; it is thus assumed that women who continue (or indicate that they would continue) to use a treatment are satisfied.

Table A.2 Pharmaceutical treatment effectiveness parameters used in the model

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 who discontinue treatment following a successful cycle of treatment	0.026	—	*Long-acting Reversible Contraception* guideline (NICE)[286] (10% of women discontinue the pill in 1 year)
Likelihood that a successful treatment continues to work	1.00	—	GDG opinion
Proportion of women who discontinue treatment when there is perceived heavy bleeding following treatment	1.00	—	GDG opinion
Proportion of women who have surgical treatment following failed pharmaceutical treatment	0.75	—	GDG opinion
LNG-IUS			
Proportion of women with LNG-IUS *in situ* after 1 year	0.68	0.61–0.75	Hurskainen[105]
Proportion of women with LNG-IUS *in situ* after 5 years	0.48	0.43–0.53	Hurskainen[104]
Proportion of women who discontinue treatment following a successful cycle of treatment:			Calculated from figures in Hurskainen[104]
Year 1	0.096	0.108–0.085	
Years 2–5	0.022	0.019–0.024	
Likelihood that a successful treatment continues to work	1.00	—	GDG opinion
Proportion of women who discontinue treatment when there is perceived heavy bleeding following treatment	1.00	—	GDG opinion
Proportion of women who have surgical treatment following failed pharmaceutical treatment	0.83	0.83–1.00	Hurskainen[104]
Insertion failure rate	0.017	—	Hurskainen[104]
Tranexamic acid			
Treatment success rate (proportion of women satisfied with tranexamic acid at 1 year)	0.77	0.67–0.87	Bonnar and Sheppard[305]
Proportion of women who discontinue treatment following a successful cycle of treatment	0.046	—	Bonnar and Sheppard[305]
Likelihood that a successful treatment continues to work	1.00	—	GDG opinion
Proportion of women who discontinue treatment when there is perceived heavy bleeding following treatment	1.00	—	GDG opinion
Proportion of women who have surgical treatment following failed pharmaceutical treatment	0.75	—	GDG opinion
NSAIDs (mefenamic acid)			
Treatment success rate (proportion of women satisfied with NSAIDs at 1 year)	0.74	0.64–0.84	Bonnar and Sheppard[305]
Proportion of women who discontinue treatment following a successful cycle of treatment	0.064	—	Bonnar and Sheppard[305]
Likelihood that a successful treatment continues to work	1.00	—	GDG opinion
Proportion of women who discontinue treatment when there is perceived heavy bleeding following treatment	1.00	—	GDG opinion

Women who continue to feel they have HMB following pharmaceutical treatment are considered to have had unsuccessful treatment. Evidence from the systematic review suggests that most women that have failed pharmaceutical treatment will undergo surgical treatment in an effort to resolve their HMB.[245,325] It is necessary to include the costs and effects of surgical treatment within the Markov model to accurately reflect the cost of failed pharmaceutical treatment.

A cost-effectiveness analysis of surgical interventions for uncomplicated menorrhagia has recently been conducted as part of the health technology assessment of endometrial ablation.[334] Data on the costs and effectiveness of surgical treatment have largely been taken from this analysis and adapted where necessary. Evidence that does not come from this analysis is taken from the systematic review of surgical interventions for HMB in Chapters 11 and 13, or from other sources of published evidence where this is missing from the systematic review. The expert opinion of the GDG was sought where no published evidence was found. Details of the clinical parameters included in the surgical treatment analysis are found in Table A.3. Uterine artery embolisation is a relatively new treatment for women with fibroids, and is not included in this model as insufficient data on which to make comparisons were available.

The outcomes of treatment in the analysis are expressed in terms of QALYs gained for each treatment. Published evidence sources were used to identify the quality of life weightings associated with living with HMB for 1 year; these values are described in detail in Table A.4. It is recognised that the utility value chosen for women with HMB refers to those referred for surgery and that this may overestimate the extent of the problem in primary care. However, sensitivity analysis undertaken to test this assumption showed that even if the utility decrement associated with HMB is low, that is it is not considered a serious problem for the woman, the relative results of the model were unchanged (see sensitivity analysis for full details).

Table A.3 Surgical treatment effectiveness parameters used in the model

Parameter	Value	Source
Initial surgical treatment		
Proportion of women who have surgical treatment following failed pharmaceutical treatment	0.75	GDG opinion
Proportion of women who undergo hysterectomy as surgical treatment for menorrhagia	0.43	Reid[606]
Proportion of women who undergo TCRE as surgical treatment for menorrhagia	0.25	Reid[606]
Proportion of women who undergo MEA as surgical treatment for menorrhagia	0.16	Reid[606]
Proportion of women who undergo TBEA as surgical treatment for menorrhagia	0.16	Reid[606]
Prevalence of fibroids	0.30	Vercellini (in Farquhar[151])
Proportion of women with fibroids who have surgery (hysterectomy or myomectomy)	0.85	GDG opinion
Complications after hysterectomy	0.086	Maresh[523]
Death after hysterectomy (direct cause)	0.00038	Maresh[523]
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[334]
Proportion of women with failed first ablation (all methods) having further treatment	1.00	Assumption in Garside[334]
Proportion of women having further treatment who have hysterectomy	0.60	Cooper[555]
Proportion of women having further treatment who have repeat ablation	0.40	Garside review of evidence[334]
Recurrence of menorrhagia following second ablation	0.10	Garside review of evidence[334]
Proportion of women with failed second ablation (all methods) having hysterectomy	0.90	Professional estimate assumed in Garside[334]

MEA = microwave endometrial ablation; TBEA = thermal balloon endometrial ablation; TCRE = transcervical resection of the endometrium.

Table A.4 Quality of life values used in the model

Health state	Value per year (95% CI)	Value per cycle (range based on 95% CI)	Source
Not well (perceived heavy bleeding)	0.50 (0.48 to 0.52)	0.125 (0.12 to 0.13)	Sculpher[554]
Well following pharmaceutical treatment (no perceived heavy bleeding)	0.84 (0.73 to 0.93)	0.21 (0.183 to 0.233)	Hurskainen[104]
Well following surgery (no perceived heavy bleeding)	0.88 (0.75 to 0.95)	0.22 (0.188 to 0.238)	Hurskainen[104]
Complications following surgery	0.50 (0.48 to 0.52)	0.125 (0.12 to 0.13)	Sculpher[554]

Quality of life scores for a reduction in heavy bleeding are estimated to be the same for all pharmaceutical treatments – it is assumed that the quality of life refers to the state of no heavy bleeding following pharmaceutical treatment, rather than to the effect of a particular drug. The adverse effect profile of each drug may have an effect on the resulting quality of life scores, although there is no evidence of this; impacts of adverse 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 between second-generation ablation techniques and hysterectomy is negligible.

The following example illustrates how QALYs are calculated in this model. Heavy menstrual bleeding is associated with a quality of life of 0.50 – that is, patients who suffer from this illness have reported that they feel a loss in terms of quality of life that is equivalent to half a year at full health.[554] During the initial 3 month cycle of the model spent in the 'not well' state, the patient accrues 0.125 QALYs (0.50 QALYs per year/four cycles per year). If the treatment is successful, the patient moves to the 'well following pharmaceutical treatment' state. During each subsequent model cycle spent in this state, the patient accrues 0.82 QALYs per full year, or 0.21 QALYs for that cycle.[104] The QALYs accrued in each cycle are then summed to give the total number of QALYs for that patient during the 5 year period of the model. Like costs, QALYs are discounted at 3.5% per annum (0.078% per cycle) to reflect the greater value attached to health gains made in the present relative to those made in the future.

Treatment costs

This analysis assumes an NHS perspective for the estimation of costs, as required by NICE guidance. Costs include the medical management of menorrhagia in a primary care setting and surgical treatment in a secondary care setting. In line with NICE recommendations, this analysis does not consider costs to the patient associated with the condition or its treatment (such as time off work or transportation to and from appointments). All costs are discounted at 3.5% per annum as recommended by NICE.

The costs of pharmaceutical treatments for HMB comprise the costs of individual medicines and devices, and the costs associated with the initial GP consultation, the fitting of devices where appropriate, routine follow-up consultations and a consultation if a decision is taken to discontinue treatment. Costs associated with the management of adverse effects from pharmaceutical treatment are not included in full, as there is insufficient evidence upon which to draw. However, the impact of adverse effects on quality of life is captured in part by the discontinuation rate of treatments. The costs for pharmaceutical treatment are detailed in Table A.5.

When pharmaceutical treatment fails, many women will undergo surgical treatment. Women referred for specialist care will require investigations to explore the cause of the HMB, followed in most cases by surgery. Investigations will involve consultation with a specialist and an ultrasound examination to exclude any intrauterine pathology and to identify fibroids. Surgical treatment is dependent on the results of the imaging examination and subsequent diagnosis. The costs for surgical treatment, including diagnostic investigations, are detailed in Table A.6.

The source for each element of the costs for both medical and surgical components of the model is included in Tables A.5 and A.6. Where possible, costs have been taken from published sources. The costs associated with imaging are taken from analysis conducted for this guideline, where the cost-effectiveness of diagnostic imaging is considered. All costs have been adjusted in line with the Hospital and Community Health Service index to 2004 prices. Some costs are subject to uncertainty and this is addressed in the sensitivity analysis.

Table A.5 Cost data for pharmaceutical treatments used in the model

Parameter	Cost (£)	Range (£)	Source
COC pill			
Initial GP consultation (10 minutes)	24.00	—	PSSRU
3 month follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Routine annual follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Cost per model cycle of COC pill (levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms)[a]	8.31	7.44–9.18	BNF
Initial stage cost	56.31	55.44–57.18	Includes cost of initial GP consultation, 3 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
LNG-IUS			
Cost of device	83.16	—	BNF
Initial consultation and fitting:		—	Costs: PSSRU
GP (30 minutes)	72.00		Length: GDG opinion/LARC
practice nurse (10 minutes)	4.30		
Sterile pack for insertion	18.20	—	LARC
4–6 week follow-up consultation:		—	Costs: PSSRU
GP (10 minutes)	24.00		Length: GDG opinion/LARC
practice nurse (10 minutes)	4.30		
3 month follow-up GP consultation 10 minutes)	24.00	—	Costs: PSSRU Length: GDG opinion/LARC
Consultation for removal:		—	Costs: PSSRU
GP (10 minutes)	24.00		Length: GDG opinion/LARC
practice nurse (10 minutes)	4.30		
Routine annual follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Sterile pack for removal	3.17	—	LARC
Initial stage cost	229.66	206.69–252.63	Includes cost of initial GP consultation, 3 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			
Initial GP consultation (10 minutes)	24.00	—	PSSRU
3 month follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Cost per model cycle of tranexamic acid (based on 28 pills per cycle)	20.16	17.28–23.04	BNF; base case reflects median drug cost
Routine annual follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Initial stage cost	68.16	65.28–71.04	Includes cost of initial GP consultation, 3 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 (mefenamic acid)			
Initial GP consultation (10 minutes)	24.00	—	PSSRU
3 month follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Cost per model cycle of mefenamic acid (based on 45 pills per model cycle) – 500 mg, 21 tablet pack = £2.21	4.74	—	BNF 50
Routine annual follow-up GP consultation (10 minutes)	24.00	—	PSSRU
Initial stage cost	52.74	47.47–58.01	Includes cost of initial GP consultation, 3 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

BNF = *British National Formulary* 50 (September 2005); COC = combined oral contraceptive; LARC = *Long-acting Reversible Contraception* guideline (NICE);[286] PSSRU = *Unit Costs of Health and Social Care* (Personal Social Services Research Unit) 2005.

[a] 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.

Table A.6 Cost data for surgical treatments used in the model

Parameter	Cost per unit (£)	Source
Initial consultation (20 minutes)	27.66	PSSRU
Second consultation (20 minutes)	27.66	PSSRU
Preoperative clinic with nurse (20 minutes)	10.00	PSSRU
Full blood count	3.06	Royal Free Hospital
Transvaginal ultrasound (TVS)	107.49	Critchley[69] and guideline analysis of imaging techniques
Cost per surgery (hysterectomy or myomectomy)	2762.88	Lumsden (unpublished data)
Cost per TCRE treatment	1324.53	Garside[334]
Cost per MEA treatment	1123.22	Garside[334]
Cost per TBEA treatment	985.90	Garside[334]

MEA = microwave endometrial ablation; PSSRU = *Unit Costs of Health and Social Care* (Personal Social Services Research Unit) 2005; TBEA = thermal balloon endometrial ablation; TCRE = transcervical resection of the endometrium.

A.1.3 Results

The results of the economic analysis are presented in the form of incremental cost-effectiveness ratios (ICERs), which express 'additional cost per quality-adjusted life year gained' of one treatment compared with another. The estimation of this ratio allows for a direct comparison between treatments, assessing whether the additional benefit (QALYs) is worth the additional cost when switching from one treatment to another. The ICERs compare the relative cost-effectiveness of the various treatments for HMB, including watchful waiting, pharmaceutical treatment and surgical treatment.

Treatments have been ranked from least to most costly, with the baseline of no treatment listed first where appropriate. Where one treatment is less costly and provides greater benefit than another treatment, the first treatment is said to dominate the alternatives. The ICERs between the non-dominated methods remaining in the analysis have been calculated.

The results of the analyses of the Markov model, for a cohort of 1000 women with uncomplicated HMB, are presented in Tables A.7, A.8 and A.9. Table A.7 shows the results when all pharmaceutical treatments are compared with watchful waiting, Table A.8 compares hormonal treatments with surgical treatment, and Table A.9 compares non-hormonal treatments with watchful waiting.

All pharmaceutical treatments versus watchful waiting

All pharmaceutical 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

Table A.7 Summary of the cost per QALY analysis for all pharmaceutical treatments at 5 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 (mefenamic acid)	1,529,051	351,141	3699.38	–119.50	Dominated by LNG-IUS
COC pill	1,714,601	536,692	3610.71	–208.18	Dominated by LNG-IUS

Table A.8 Summary of the cost per QALY analysis for hormonal pharmaceutical treatments at 5 years for a cohort of 1000 women (hormonal treatments compared with surgery)

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	Dominated by LNG-IUS
COC pill	1,714,601	536,692	3610.71	–208.18	Dominated by LNG-IUS

Table A.9 Summary of the cost per QALY analysis for non-hormonal pharmaceutical treatments at 5 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	—	—
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

and is less costly over 5 years than any of the other treatment options. The cost per additional QALY for choosing LNG-IUS in preference to no pharmaceutical treatment is £840. Sensitivity analysis of these comparisons 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 pharmaceutical treatment is the only cost-effective strategy.

Hormonal treatments versus surgery

The contraceptive pharmaceutical treatments are compared only with surgical treatments, as a loss of fertility is generally a consequence of surgical treatments (apart from myomectomy for women with uterine fibroids).

The LNG-IUS is the least costly of the three options compared. Both direct referral for surgery and the combined oral contraceptive (COC) pill accrue fewer QALYs at a greater cost than LNG-IUS. As reported in the systematic review of hormonal treatments (Chapter 8), little clinical evidence of sufficiently high quality was found that evaluated the COC pill as a treatment for menorrhagia, and therefore the results should be interpreted with caution. 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

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 more cost-effective option.

A.1.4 Sensitivity analysis

The development of a decision-analytic model is often subject to a degree of uncertainty in the value of the parameters used to populate the model. To help understand how this uncertainty affects the results of the analysis it is useful to explore how sensitive the model is to changes in all or some of the parameters. Sensitivity analysis is simply the process of altering the value of one or more parameters used in a decision-analytic model and recalculating the results. The results of the adjusted model are then compared with the baseline results. The differences between the results indicate how much influence a given parameter can have on the outcome of a model: the greater the difference, the more influential the parameter is likely to be.

Many parameters used in the above analysis of pharmaceutical treatments for HMB are subject to uncertainty. The sensitivity of the model to a number of these parameters is explored through a series of one-way and threshold analyses. Parameters examined in the analysis include:

- utility values
- treatment effectiveness/discontinuation rates
- cost of pharmaceutical treatments
- cost of surgical treatments.

Further analysis has been undertaken to examine the threshold level of effectiveness required for a second pharmaceutical treatment to be cost-effective following a failed first pharmaceutical treatment.

Utility values and preference for hysterectomy

One area that was considered to be of potential importance to the results of the model analysis was the utility loss of a woman with HMB. This varies substantially between patients, ranging from a utility value of 0.00 to 0.95 (where full health equals a utility of one). The base-case analysis assumes the mean value of 0.50 for the utility associated with having HMB. One-way sensitivity analysis was undertaken to test whether this assumption was valid.

Additionally, many women place a high value on retaining their uterus (though not necessarily fertility) and have a strong preference for avoiding hysterectomy as a treatment to resolve the problem of menorrhagia. Although this preference is partially captured in the model by the proportion of women who are assumed to not undergo surgery as treatment (see Table A.3), sensitivity analysis can establish the impact of assuming that women have a strong preference for retaining their uterus, by assuming that no woman will have hysterectomy as the first-line pharmaceutical treatment for uncomplicated menorrhagia.

The initial analysis examines what would happen in the case of a typical woman who experienced a mean utility for menorrhagia of 0.50 and who had no expressed preference to avoid hysterectomy. Sensitivity analysis has been used to examine four alternative circumstances:

- the utility decrement from HMB is high and there is a strong preference to avoid hysterectomy
- the utility decrement from HMB is high and there is no strong preference to avoid hysterectomy
- the utility decrement from HMB is low and there is a strong preference to avoid hysterectomy
- the utility decrement from HMB is low and there is no strong preference to avoid hysterectomy.

Utility values in this analysis were varied by two standard deviations from the mean in either direction: the minimum utility value used was 0.19 and the maximum utility value used was 0.81. These figures were derived from a study that examined the cost–utility of hysterectomy compared with TCRE (Table A.4).

In those women for whom there is no strong preference to avoid hysterectomy, changes in the utility value associated with HMB have little impact on the results of the model. When utility associated with HMB is low (0.19), LNG-IUS remains the dominant treatment strategy, with a cost of £479 per additional QALY when compared with no treatment. LNG-IUS remains the only cost-effective treatment strategy until utility associated with HMB is 0.79. When utility is equal to or greater than 0.80, the COC pill may be cost-effective compared with LNG-IUS: at a utility value of 0.80, the COC pill generates each additional QALY at a cost of £24,510. For nearly all women the LNG-IUS will remain the cost-effective treatment strategy.

To examine the impact of changes in the utility value for women where there is a strong preference to avoid hysterectomy, an additional assumption was made that no woman will have a hysterectomy as the first-line surgical treatment for uncomplicated menorrhagia (although women with fibroids will be assumed to continue to undergo surgical treatment consisting of either myomectomy or hysterectomy). Hysterectomy will only be assumed to occur after a failed endometrial ablation. The proportion of endometrial ablations performed by alternative methods (MEA, TBEA and TCRE) remains constant.

The model is also not sensitive to changes in the utility value associated with HMB when it is assumed that there is a strong preference to avoid hysterectomy. When the utility value is at the minimum point in the range tested (0.19), LNG-IUS costs less and generates a greater number of QALYs than any other treatment, and dominates all other treatments at all other utility values tested under this scenario until the utility is greater than 0.76. Above this level of utility, the COC pill is more costly, but more effective, than the LNG-IUS. When the utility value is equal to 0.79, the incremental cost-effectiveness ratio for the COC pill compared with the LNG-IUS is £26,541 per QALY.

Under certain conditions, where the utility of a woman as a result of menorrhagia is relatively high (greater than 0.75), the COC pill may be a cost-effective alternative to the LNG-IUS. However, the utility value required for the COC pill to be cost-effective falls within the confidence limits assumed for the utility value associated with successful pharmaceutical treatment for menorrhagia.

No other treatment strategy was cost-effective at any level of utility assumed in the analysis. The model is thus not sensitive to differences in the strength of a woman's preference for avoiding hysterectomy.

Treatment effectiveness/discontinuation rates

For many women, pharmaceutical treatment will not be effective in reducing menstrual blood loss to an acceptable level. Following ineffective pharmaceutical treatment, many women will go on to have surgical treatment for uncomplicated menorrhagia, such as hysterectomy or endometrial ablation. Given the high costs of surgical intervention, it was believed that the initial treatment success rate of an intervention may have an impact on the overall cost of first-line medical therapies.

There is uncertainty in the assumed discontinuation rate over 5 years for tranexamic acid and NSAIDs. Data on discontinuation for these treatments was only available for 1 year, and the same annual rate was assumed for the 5 year time horizon of the model. In one-way sensitivity analysis, the discontinuation rates for these were varied by ± 10% of their baseline value. The model was not sensitive to variation in the discontinuation rates for either treatment and both were dominated by LNG-IUS for all discount rates considered.

A threshold analysis was conducted to investigate whether there is a value for the discontinuation rate for each treatment at which tranexamic acid, as the most cost-effective non-hormonal treatment, would be cost-effective in comparison with LNG-IUS. The discontinuation rate assumed in the base-case analysis for tranexamic acid was 2.4% per cycle (9.1% annually). The sensitivity analysis showed that if the discontinuation rate for tranexamic acid were equal to 1.8% per cycle (6.9% annually), this treatment would generate a greater number of QALYs at a greater cost, when compared with LNG-IUS, with an ICER of £16,661. If the discontinuation rate per period for tranexamic acid were equal to 1.3% or less (5.2% or less annually), tranexamic acid would generate more QALYs at lower cost than LNG-IUS.

A lack of high-quality evidence regarding the initial treatment success rate for the COC pill required that an effectiveness rate be estimated in the model. For the base-case analysis, effectiveness was estimated using a triangle distribution, with a minimum value of 0.10 and a maximum value of 0.77. The maximum value chosen was the highest effectiveness rate of other pharmaceutical treatments. The minimum value was selected based on clinical expertise as a likely minimum value. The sensitivity analysis tests the cost-effectiveness of the COC pill at a range of fixed effectiveness rates within this same range. At all effectiveness rates tested, the COC pill generates fewer QALYs at greater cost than the LNG-IUS.

Pharmaceutical treatment costs

The model of pharmaceutical treatments developed for this guideline examined the cost-effectiveness of these treatments over a period of 5 years. Although the cost per model cycle for each treatment may be relatively low, it was felt that given the 5 year time frame of the model, changes in the cost of a pharmaceutical treatment may have an influence on the relative cost-effectiveness between treatments

Over 5 years, the total cost for each medicine at their discounted present value was £222.69 for NSAIDs, £284.61 for the COC pill, £325.31 for LNG-IUS and £490.13 for tranexamic acid, While the LNG-IUS has a higher cost in the initial model period owing to the cost of the device and its insertion, this difference is less pronounced for two of the treatment strategies over the 5 year time period, and one treatment is more costly.

To account for the potential variation in costs for each strategy, a series of one-way sensitivity analyses was conducted. The cost of the initial treatment cycle as well as the cost of each subsequent treatment cycle was varied for each pharmaceutical treatment by the values indicated in Table A.5. Overall, the model was not sensitive to changes in the cost of pharmaceutical treatments. The LNG-IUS generated more QALYs at a lower cost under each of the scenarios considered.

The cost in the initial cycle for LNG-IUS is significantly higher than for the other pharmaceutical treatments. Within the base-case analysis there is an assumption that the device is fitted within a GP surgery under supervision of a practice nurse. In some cases, it may be necessary

for the device to be fitted under different circumstances. A threshold analysis was undertaken to estimate at what initial cost the LNG-IUS would not be considered the most cost-effective first-line pharmaceutical treatment.

When the cost for the initial cycle of treatment is more than doubled, to £545, the LNG-IUS strategy generates more QALYs than tranexamic acid but at a greater cost; however, the ICER is just £1,069 and the LNG-IUS strategy would be considered cost-effective. When the cost of the initial cycle is £1,900, the LNG-IUS strategy generates more QALYs than tranexamic acid at a greater cost, with an ICER of £20,021. If the threshold willingness-to-pay per QALY is assumed to be £20,000, then the LNG-IUS may not be considered a cost-effective treatment when compared with tranexamic acid when the cost of the initial cycle is greater than £1,900. If, however, the maximum willingness-to-pay per additional QALY is assumed to be £30,000, the initial cycle cost of the LNG-IUS strategy would have to exceed £2,500 before it would not be considered cost-effective when compared with no treatment.

Surgical treatment

In those instances where pharmaceutical treatment does not resolve HMB to the woman's satisfaction, she may be offered the option of surgical treatment. The analysis of surgical procedures used as the comparator in the model comprises a variety of methods which reflect current surgical treatment practices, including hysterectomy and endometrial ablation for uncomplicated menorrhagia, and myomectomy and hysterectomy for women who have fibroids.

The structure of the model is based on the assumption that all surgical treatments will occur within a single model cycle, as the average waiting time for hysterectomy is 83 days and for ablation 94 days (one model cycle is roughly 91 days). As a result, the total number of QALYs generated by surgical treatment in any model strategy may be overestimated. This overestimate of QALYs is likely to be a result of women requiring repeat ablation or hysterectomy following a failed ablation, as the subsequent procedure is unlikely to occur within the same model cycle. However, only a small number of women in each medical strategy will have a failed surgical treatment, and this assumption is unlikely to have a significant impact on the relative results of the model. In the base-case analysis, LNG-IUS generates a greater number of QALYs than surgery, at a lower cost, and any change to the model to reflect waiting times for repeat procedures would result in the surgical comparator generating fewer QALYs than before, with little difference in cost.

While less costly than hysterectomy, ablative methods for the treatment of uncomplicated menorrhagia are not always successful in reducing blood loss to acceptable levels. In some instances, further treatment is required; this is either by repeat ablation or by hysterectomy. Despite this, ablative methods have been shown to be cost-effective when compared with hysterectomy even when accounting for rates of re-treatment. As with all surgical methods, although the costs and benefits of ablation, including repeat procedures, are assumed to be incurred in a single model cycle, the relative results are highly likely to remain unaffected.

Surgical treatment costs

The model was not sensitive to variation in the costs of any of the surgical treatments. At no values within the range of costs associated with surgical treatments that were considered (Table A.6) in one-way sensitivity analyses did the relative cost-effectiveness of the treatment strategies vary. LNG-IUS dominated all other strategies under all circumstances when surgical costs were varied.

A.2 Cost-effectiveness of using more than one pharmaceutical treatment before referral to surgery

The use of a second or third pharmaceutical treatment in the event of an initial pharmaceutical treatment failing is an important part of clinical practice. However, no evidence assessing the effectiveness of multiple pharmaceutical treatments was identified in the literature review. In the absence of this evidence, it would be unreasonable to assume that the treatment effect of subsequent treatments is independent of the result of the initial treatment. To address this question, the Markov model used in the earlier analyses has been modified to estimate the

minimum treatment effect required for a second pharmaceutical treatment to be considered cost-effective against strategies that involve only a single pharmaceutical treatment prior to referral for surgery.

Only those treatments that have been recommended as first-line pharmaceutical treatments in this guideline have been considered as first-line treatments in this analysis. Two strategies assuming there was no preference for contraceptive benefit were assessed: one strategy was assessed where it was assumed that contraceptive benefit was sought, and one strategy was assessed for those women wishing to avoid contraceptive benefits. The four additional strategies considered were thus:

- LNG-IUS followed by the COC pill
- LNG-IUS followed by tranexamic acid
- LNG-IUS followed by mefenamic acid
- tranexamic acid followed by mefenamic acid.

A key assumption in this analysis is that a subsequent pharmaceutical treatment is only considered where the first treatment has failed in the initial model cycle. Strategies involving two pharmaceutical treatments are not compared with one another, as there is no accepted level of effectiveness for any treatment, and thus no basis for comparison.

A.2.1 Results

For each two-treatment strategy, there is a level of clinical effectiveness where the strategy is more effective and less costly than a single treatment strategy. Where this is the case, the strategy should be adopted if it is believed that the treatment is likely to be effective in that proportion of women. If that is not the case, the treatment should only be adopted if the expected level of effectiveness generates a cost saving of greater than £20,000 per QALY. The strategy requiring the lowest level of clinical effectiveness for the second pharmaceutical treatment in order to be considered cost-effective is that of LNG-IUS followed by tranexamic acid. This strategy should considered cost-effective if tranexamic acid is effective in at least 13% of women where LNG-IUS has failed. At this level of effectiveness, the strategy is cost saving – it generates fewer QALYs but at a lower cost.

The level of clinical effectiveness for each strategy where it costs less and generates a greater number of QALYs is:

- 0.25 for LNG-IUS followed by tranexamic acid when compared with LNG-IUS alone
- 0.28 for LNG-IUS followed by COC pill when compared with LNG-IUS alone
- 0.33 for LNG-IUS followed by NSAIDs when compared with LNG-IUS alone
- 0.38 for tranexamic acid followed by NSAIDs when compared with tranexamic acid alone.

For a strategies-considered cost saving, at a threshold willingness-to-pay value of £20,000 per QALY, then:

- LNG-IUS followed by tranexamic acid is cost-effective when the additional treatment is effective in approximately 13% of the remaining women
- LNG-IUS followed by the COC pill is cost-effective when the additional treatment is effective in approximately 15% of the remaining women
- LNG-IUS followed by NSAIDs is cost-effective when the additional treatment is effective in approximately 15% of the remaining women
- Tranexamic acid followed by NSAIDs is cost-effective when the additional treatment is effective in approximately 20% of the remaining women.

A.3 Cost-effectiveness of imaging for exclusion of structural abnormalities of the uterus in women with uncomplicated menorrhagia

A.3.1 Methods

When women feel that pharmaceutical 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 women 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 (TVS) and hysteroscopy. Saline infusion 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.1), specialised decision analysis software. Prior to visualisation, women in the model were assumed to have one of two health states: no intrauterine pathology, or any intrauterine pathology. Following the examination, the women 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 diagnosis, as the range of potential pathologies and treatments is beyond the scope of this guideline.

It will not be possible to conduct a successful visualisation in all patients. Where visualisation is unsuccessful, patients drop out of the pathway and do not re-enter the model, as evidence was not found to estimate the likelihood of success for a second attempt at visualisation using the techniques under consideration. In the absence of specific evidence, independence between the first result and second result cannot be assumed. Full test costs are still incurred for unsuccessful visualisations.

Clinical effectiveness

Estimates of the diagnostic accuracy of each imaging method are taken from a systematic review[151] of investigations for abnormal uterine bleeding (AUB) in premenopausal women. The original source of each estimate is indicated in Table A.10. Individual studies included in the review were not retrieved. Estimates of the number of successful visualisations are taken from a health technology assessment examining outpatient procedures for the investigation of women with AUB.[69]

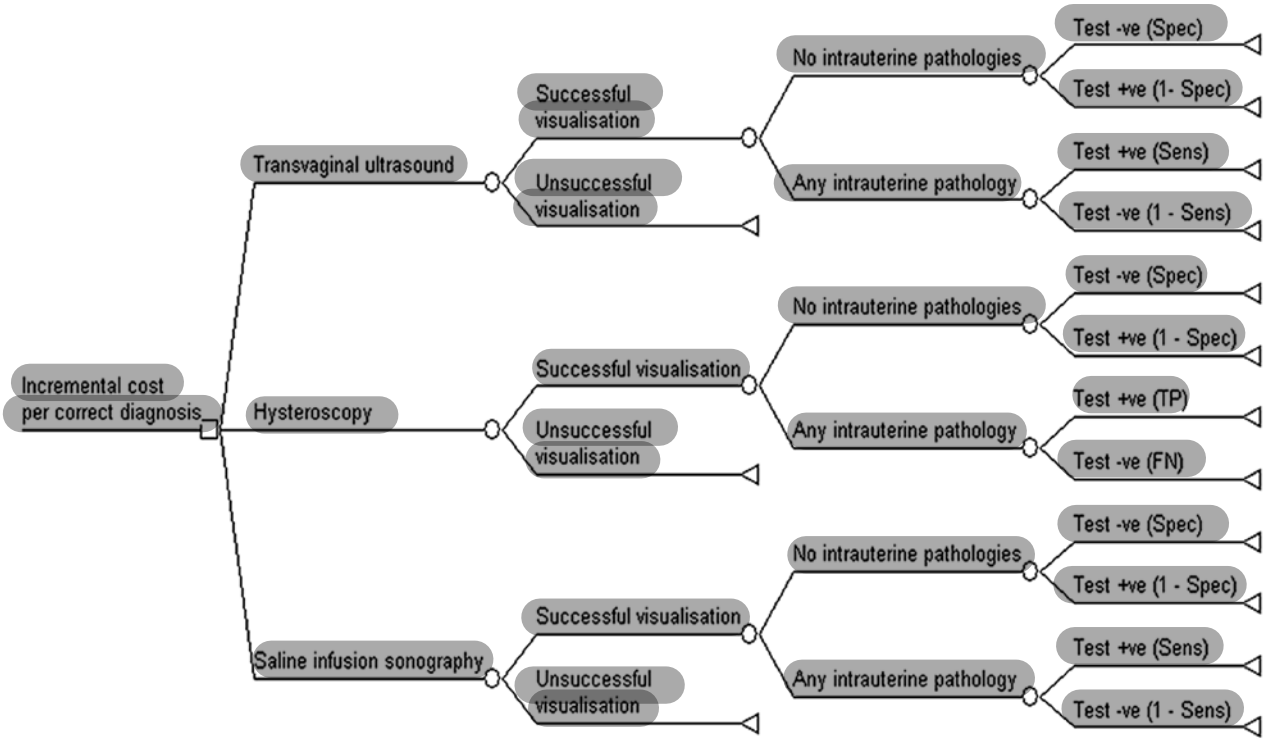

Figure A.1 Decision tree for evaluating the cost-effectiveness of imaging for investigating intrauterine pathology

Table A.10 Diagnostic test effectiveness and range for sensitivity analysis

Diagnostic test	Value (source)	Range (source)
Transvaginal ultrasound (TVS)		
Sensitivity (%)	96 (Vercellini[a])	48–100 (Krampl[a]; Fedele[a])
Specificity (%)	86 (Vercellini[a])	28–100 (Bronz[a]; Fedele[a])
Successful visualisations (%)	88 (Critchley[69])	79–97 (±10%)
Saline infusion sonography		
Sensitivity (%)	87 (Schwarzler[a])	87–100 (Schwarzler[a]; Dijkhuizen[a])
Specificity (%)	91 (Schwarzler[a])	50–100 (Ossola[a]; Gronlund[a])
Successful visualisations (%)	83[b]	Minimum range of hysteroscopy to maximum range of TVS
Hysteroscopy		
Sensitivity (%)	90 (Schwarzler[a])	90–97 (Schwarzler[a]; Widrich[a])
Specificity (%)	91 (Schwarzler[a])	62–93 (Ossola[a]; Widrich[a])
Successful visualisations (%)	77 (Critchley[69])	70–85 (±10%)
Prevalence of uterine pathology		
A priori probability of any intrauterine pathology (%)	61 (Vercellini[a])	—

[a] Cited in Farquhar.[151]
[b] The rate of successful visualisation for saline infusion sonography was not identified in the review of the literature and has been estimated. This assumption is tested in the sensitivity analysis.

Costs

Costs are estimated at 2004 prices, with costs from earlier years being adjusted according to the Hospital and Community Health Services pay and prices index. The perspective adopted for the economic evaluation is that of the NHS, in line with NICE guidance on economic evaluations for guidelines. Costs included in the model comprise the staff and equipment costs necessary to carry out the described examinations. Although the guideline does not address service configuration, assumptions are made in the model about the setting in which each procedure is undertaken. The model does not consider the future management of patients following examination. Owing to the range of intrauterine pathologies requiring varied treatment regimes, the majority of which fall outside the scope of this guideline, it is not possible in this analysis to

Table A.11 Cost of imaging procedures

Imaging method	Cost per unit (£)	Range (£)	Source
Transvaginal ultrasound (TVS)			
Gynaecological outpatient appointment	61.56	—	Critchley[69]
Outpatient ultrasound session	45.93	—	Critchley[69]
Total cost of TVS (per procedure)	107.49	96.74–118.24	Range is ±10% of total cost
Saline infusion sonography			
Gynaecological outpatient appointment	61.56	—	Critchley[69]
Outpatient ultrasound session	45.93	—	Critchley[69]
Consumables	37.62	0.00–100.23	Cost of TVS plus 35%; Dijkhuizen[556]
Total cost of saline infusion sonography (per procedure)	145.11	107.49–209.72	Range is based on maximum and minimum costs of TVS and hysteroscopy
Hysteroscopy			
Gynaecological outpatient appointment	61.56	—	Critchley[69]
Outpatient hysteroscopy (with reusable sheath)	148.16	—	Critchley[69]
Total cost of hysteroscopy (per procedure)	209.72	188.75–230.69	±10% of total cost

conduct a cost-effectiveness analysis of the diagnostic methods under consideration using quality-adjusted life years as the outcome.

Saline infusion sonography is uncommon in the NHS, and no studies providing UK costs were identified. Costs for this procedure have been estimated as for TVS plus the additional costs associated with the saline infusion process. One comparison of imaging methods[556] estimated that the costs of saline infusion sonography would exceed those of TVS by approximately 35%. In the absence of published UK costs, the cost of saline infusion sonography has been estimated as that for TVS plus 35%. Sensitivity analysis on this cost has been undertaken to test the validity of this assumption.

The analysis assumes that the hysteroscopy procedure takes place in an outpatient setting with a reusable sheath. This is the least costly option, although the cost of outpatient hysteroscopy is explored in the sensitivity analysis to allow for variation in the cost of reusable versus disposable hysteroscopy equipment. Inpatient hysteroscopy is not explicitly considered; costs in an inpatient setting are greater although there is no evidence that accuracy differs between settings.

A.3.2 Results

The results of the analysis for a hypothetical cohort of 1000 women are presented in Table A.12, in order from the least to the most costly, as both TVS and hysteroscopy are in routine use at present and neither can be considered the standard method against which the other techniques can be compared. In the analysis, both saline infusion sonography and hysteroscopy are dominated by TVS; that is, TVS is both less costly and more accurate than the other methods compared here.

Table A.12 Cost per correct diagnosis at first visualisation (for a cohort of 1000 women)

Imaging method	Total cost (£)	Correct diagnoses	Incremental cost (£)	Incremental effect (QALYs)	ICER	Cost per correct diagnosis (£)
Transvaginal ultrasound (TVS)	107,490	810	—	—	—	132.63
Saline infusion sonography	145,100	735	37,610	–75	Dominated by TVS	197.42
Hysteroscopy	209,720	696	102,230	–114	Dominated by TVS	301.32

The cost per correct diagnosis for TVS is £132.63, for saline infusion sonography it is £197.42 and for hysteroscopy £301.32. Using TVS results in 810 correct diagnoses (at a total cost of £107,490), compared with just 735 correct diagnoses with saline infusion sonography (£145,100) and 696 correct diagnoses with hysteroscopy (£209,720). Incremental cost-effectiveness ratios are not calculated, as TVS is less costly and more accurate than the other methods and should be recommended as the standard imaging method for excluding structural abnormalities in women with HMB.

A.3.3 Sensitivity analysis

Many of the parameters in this model are subject to uncertainty and a number of one-way and threshold sensitivity analyses were undertaken to test the robustness of the model. The ranges of the effectiveness and cost parameters included in the sensitivity analyses are listed in Tables A.10 and A.11.

Costs

No published studies provided data on the cost of saline infusion sonography in an NHS setting, and the GDG was unable to identify a source to estimate the cost of the procedure. A comparison of TVS with saline infusion sonography in the Netherlands, with costs estimated in US dollars, found that saline infusion sonography was 35% more costly than TVS, and as such, the costs for saline infusion sonography were estimated in a similar manner for the purposes of this model.[556]

To test the validity of this assumption, the costs for saline infusion sonography were varied across a range of figures. When the cost is equal to that of TVS, saline infusion sonography provides each correct diagnosis at a cost of £146.24, still greater than that of TVS. In order for saline infusion sonography to provide each correct diagnosis at the same cost as TVS, each procedure would have to cost only £97.48. Given the additional expense incurred with saline infusion sonography compared with TVS, this value is unrealistic. There is thus no cost at which saline infusion sonography will be cost-effective compared with TVS

Hysteroscopy was the most costly and least effective of the three imaging techniques under consideration. The assumptions in the initial analysis used the least costly method of performing a hysteroscopy, using a reusable sheath in an outpatient setting. This method was more costly and less effective than TVS, so methods with additional costs (using disposable sheaths or performing the procedure in an inpatient setting) are not considered. A threshold analysis of the model shows that in order for hysteroscopy to generate the same cost per correct diagnosis, the procedure would have to cost only £92.32.

Effectiveness

The greatest range of uncertainty in the model parameters is in the diagnostic accuracy of each imaging test. A systematic review found a wide range in the reported sensitivity and specificity for each test. The figures used in the analysis are assumed to be the best available estimates and are drawn from this review based on the evidence grade and sample size of the individual studies as reported in the review. Given the wide range of published figures, a series of one-way and two-way sensitivity analyses has been conducted to test the impact of variation in these parameters on the results of the model.[151]

TVS had the widest range of reported results for sensitivity (48–100%) and specificity (28–100%). Under one-way sensitivity analysis, when sensitivity is varied to the minimum and maximum reported values, the cost per correct diagnosis ranges from £194.44 to £129.20, and when specificity is varied to the minimum and maximum reported values, the cost per correct diagnosis ranges from £175.80 to £125.20. Under a two-way sensitivity analysis, when sensitivity and specificity are varied to the maximum reported values, the cost per correct diagnosis is £122.15 (880 correct diagnoses). When the sensitivity and specificity of TVS are varied to their minimum reported values, the cost per correct diagnosis is £303.85 (354 correct diagnoses). Under these conditions, TVS is more costly and less accurate than either saline infusion sonography or hysteroscopy, although the difference with hysteroscopy is small, and the model may not be sensitive enough to accurately detect such a difference.

The sensitivity of saline infusion sonography ranged from 87% to 100%. The lower estimate is that used in the initial analysis. Specificity ranged from 50% to 100%. When the sensitivity is varied to the maximum reported value, the cost per correct diagnosis is £181.19 (801 correct diagnoses), and when the specificity is varied between the minimum and maximum reported values, the cost per correct diagnosis is £240.91 (602 correct diagnoses) and £189.89 (764 correct diagnoses), respectively. Under a two-way sensitivity analysis, when both the sensitivity and specificity of saline infusion sonography are varied to their minimum reported values, the cost per correct diagnosis is £240.91 (602 correct diagnoses). Under these circumstances, saline infusion sonography is less effective and more costly than TVS.

When sensitivity and specificity of saline infusion sonography are varied to the maximum reported values, the cost per correct diagnosis is £174.83 (830 correct diagnoses). Under these conditions, when compared with the initial analysis of TVS, saline infusion sonography generates an additional 20 correct diagnoses at an incremental total cost of £37,620, giving a cost per additional correct diagnosis of saline infusion sonography of £1,927.25 when compared with TVS results.

The reported sensitivity for hysteroscopy ranged from 90% (as used in the initial analysis) to 97% and specificity ranged from 62% to 93%. Varying the sensitivity to the maximum value, hysteroscopy generates 729 correct diagnoses at a cost of £287.73 each. At the minimum reported value for the specificity of hysteroscopy, it generates 609 correct diagnoses at a cost of £344.42 per correct diagnosis and at the maximum reported specificity it generates 702 correct diagnoses at a cost of £298.74 per correct diagnosis. When the sensitivity and specificity are both varied to the maximum reported values, hysteroscopy generates 735 correct diagnoses at a cost of £285.38

each. At no values of the reported sensitivity and specificity of hysteroscopy is this method cost-effective when compared with the initial results of TVS.

Only one study was identified that estimated the proportion of successful visualisations using hysteroscopy and TVS. No published studies were identified that estimated the proportion of successful visualisations using saline infusion sonography, and this value was estimated as being midway between the values for the other two procedures. Sensitivity analyses using the ranges estimated in Table A.10 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 infusion sonography is varied to the maximum value tested of 97% (Table A.10), it generates 49 additional correct diagnoses at an additional cost of £37,967 when compared with TVS, with an incremental cost per additional correct diagnosis of £774.84.[69]

Limitations of the 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 all 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 performing the imaging as well as that of the individual who interprets the results. The model is unable to account explicitly for the competencies of the various operators involved throughout each imaging process. Some element of operator competency may be captured in the sensitivity analysis, through the range of sensitivity and specificity values examined for each procedure. It is not possible, however, to determine what proportion, if any, of the reported ranges are related to operator competency and what is due to other factors. Operator competency may also be captured to some extent in the rate of successful visualisations assumed in the model although, again, it is not possible to quantify, based on the available evidence, what proportion of failed procedures is due to the operator.

Another potential limitation of the model as presented here is the choice of outcome measure. The preferred methodology according to the NICE technical manual is to present outcomes in terms of quality-adjusted life years (QALYs). Given the range of pathologies under consideration, and the associated range of treatment pathways, the information requirements to estimate the true cost per QALY of each diagnostic method was beyond the scope of the guideline. This may have some influence over the results, as some women may undergo unnecessary treatment, while others will not be given required treatment, based on false results following diagnosis. By measuring the results in cost per correct diagnosis, the model may not reflect the true long-term costs and outcomes associated with each diagnostic method.

Not measuring the outcome of the model in QALYs may also inaccurately reflect the quality of life gain or loss in the short-term, as the chosen outcome does not account for the disutility of undergoing an invasive diagnostic procedure. This may be reflected to a certain extent in the rates of failure, as the more invasive procedures are successfully completed less often than the less invasive procedures. Although this is unlikely to have a bearing on the longer term analysis incorporating the full effect of treatment following diagnosis, in the absence of such evidence it must be considered.

A final limitation concerns the uncertainty in the cost and effectiveness parameters assumed in the analysis of saline infusion sonography. This procedure, although used in other European countries and the USA, is uncommon within the NHS. As a result, there is a shortage of high-quality UK-based evidence regarding its accuracy and cost. Although the sensitivity analysis suggests that under certain, limited, scenarios it may be cost-effective when compared with TVS, until further research is undertaken, it cannot be considered a cost-effective option for the diagnosis of intrauterine pathologies in women with heavy menstrual bleeding.

Appendix B

Competencies

Introduction

Competencies of clinicians performing procedures to treat HMB were considered within a framework based on existing models of quality assurance, i.e. with consideration of:

- inputs (how competence is achieved)
- process/service (how competence is maintained)
- how it is measured (e.g. auditing competence based on quality standards).

This framework was not meant to be exclusive, and if other factors appeared relevant they would be included.

B.1 Becoming competent – training standards

The process for an individual to become competent in a procedure is usually based on their undergoing suitable education and training. Given that there can be a wide variation in the standards of education and training courses provided, these courses must be recognised by regulatory or governing bodies as providing training and education to a suitable level.

The results of the literature search provided very limited data, especially on training standards. This is unsurprising given that most training standards are published by governing bodies rather than as research articles. The relevant governing bodies were contacted about education and training standards: the Royal College of Obstetricians and Gynaecologists (RCOG), the Royal College of Radiologists (RCR), the Society and College of Radiographers (SCoR) and the British Society for Gynaecological Endoscopy (BSGE). In addition, the GDG also provided information on training and education.

In relation to surgical skills, the GDG outlined a series of basic requirements.

Knowledge:

- specific indications for intervention
- required preparation for intervention, including preoperative investigations
- outcomes and complications of proposed procedure
- anatomy relevant to procedure
- steps involved in procedure
- knowledge of alternative operative strategies if difficulties are encountered
- potential complications
- outcomes of procedure
- likely post-procedure progress
- physiological and pathological changes in condition as a result of the procedure.

Other generic skills:

- be able to explain procedures and possible outcomes to patients and family and take informed consent
- possess the necessary hand–eye dexterity to complete the procedure safely and efficiently, demonstrating appropriate use of assistance
- communicate effectively with and manage the operative team
- assess the patient for appropriate management options
- assess the patient for physiological parameters and be able to intervene appropriately to deal with changing parameters
- ability to prioritise interventions.

Attitude:

- demonstrate interest in, knowledge of, and commitment to the specialty
- recognise when to ask for advice from others
- demonstrate commitment to the multidisciplinary team working with other clinicians involved in the care of women with HMB.

Surgeons should conform to standards of good medical practice (the General Medical Council) and good surgical practice (Royal College of Surgeons, the Royal College of Obstetricians and Gynaecologists and the British Society for Gynaecological Endoscopy):

- Surgeons should participate in local and national audit.
- If a surgeon undertakes any new class of procedure for which he/she does not have appropriate training then he/she should seek formal training through a process of mentoring. This includes appropriate training of the surgical team.
- Before undertaking new procedures, clinicians must notify their trust's clinical governance committee, and the audit of these new procedures should be appraised annually.
- A robust risk management structure must be in place to facilitate reporting of adverse events.
- Attention should be given to ensuring correct and complete coding of procedures for national audit programmes.
- Before utilising new materials or devices in previously established procedures, the trust's clinical governance committee should be informed.
- Any intention to undertake an evaluation of a new procedure should be registered with a relevant clinical trials database.
- The development of new techniques or modifications of established techniques should receive appropriate local ethical and clinical governance approval.
- A clinician who encounters a serious adverse event related to the use of a device or implant in the treatment of HMB should notify the Medicines and Healthcare products Regulatory Agency (MHRA), through its Serious Adverse Event (SAE) reporting process.
- New procedures/classes of procedure should be notified to the Interventional Procedures Programme at NICE through the NICE website.
- Clinicians should see enough patients per annum to maintain both non-operative and operative skills.

In addition, education and training covers clinicians committing to continuing medical education in order to maintain knowledge and skills.

B.2 Maintaining competence

Maintaining competence in a procedure requires two main elements:

- continuing training and education
- continued experience of the procedure in practice.

B.2.1 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.

B.2.2 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:[557–559]

- 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)
- thresholds for definitions of high and low volume across and within procedures differ
- causality – it is unclear whether high volume-improved outcome relationships result from greater experience or whether the highest referral rates tends to be to those clinicians or centres who have the best results.

Hospital volume and operator volume may both be important, and the relative importance may vary from one procedure to another. For some procedures, such as trauma-related reconstruction, it may be the total amount of relevant surgery that is most important rather than the specific number of particular procedures. Complexity of procedures, and whether their use is commonplace, also influences whether a difference in outcomes can be seen for a given volume.

Although the evidence tends to suggest that higher volume is associated with better outcomes, the consistency and size of the effect varies for different procedures. A systematic review of 135 studies found a significant association between higher volume (hospital or surgeon) and better outcomes in about 70% of studies; none of the studies found a significant association between higher volume of any type of surgery and poorer outcome.[558] In these studies, the definition of low or high volume varied according to the procedure, with median low volumes of up to 100–200 for coronary angioplasty or coronary artery bypass graft surgery; and median low volume values ranging from 1 to 73 for other procedures described (mainly in the region of 10–30).[558]

Secondary surgery is unusual and can be technically challenging, and a centralisation argument probably applies. The centralisation argument holds that 'practice makes perfect', so concentration of cases into fewer centres that can carry out larger numbers of procedures will result in higher standards not just of technical surgery but also of postoperative care.

B.3 Monitoring competence

The final area involves outlining the standards by which competence in undertaking a particular intervention can be monitored. Audit standards for competencies should be based upon ensuring that:

- recognised education and training has been undertaken
- continuing education and training is undertaken
- a minimum level of procedures are undertaken to maintain competence
- outcomes of procedures are within expected ranges.

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?
13. What are the indications for, effectiveness of, and cost-effectiveness of tests for excluding other conditions?
14. What are the indications for, effectiveness of, and cost-effectiveness of a full blood count to test for anaemia?

4.3.c. The guideline will provide advice on the medical management of HMB, including short- and long-term outcomes, adverse events, cost-effectiveness and subsequent treatment.

15. What are the indications for, effectiveness of, and cost-effectiveness of using antifibrinolytics for treating HMB?
16. What are the indications for, effectiveness of, and cost-effectiveness of using NSAIDs for treating HMB?
17. What are the indications for, effectiveness of, and cost-effectiveness of using etamsylate for treating HMB?
18. What are the indications for, effectiveness of, and cost-effectiveness of using the combined oral contraceptive pill for treating HMB?
19. What are the indications for, effectiveness of, and cost-effectiveness of using oral progestogens for treating HMB?
20. What are the indications for, effectiveness of, and cost-effectiveness of using injected/depot progestogens for treating HMB?
21. What are the indications for, effectiveness of, and cost-effectiveness of using intrauterine levonorgestrel-releasing systems for treating HMB?

22. What are the indications for, effectiveness of, and cost-effectiveness of using HRT for treating HMB?
23. Medical management of HMB using other pharmaceutical interventions?
24. What are the indications for, effectiveness of, and cost-effectiveness of using gonadotrophin-releasing hormone analogue for 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 whether, 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 indications for, effectiveness of, and cost-effectiveness of using dilatation and curettage for treating HMB?
28. What are the indications for, effectiveness of, and 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 indications for, effectiveness of, and cost-effectiveness of using radiological interventions for treating HMB?

4.3.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).

30. What are the indications for, effectiveness of, and cost-effectiveness of using myomectomy for treating HMB?
31. Are there any indications for using hysterectomy as first-line treatment for HMB?
32. What are the indications for, effectiveness of, and cost-effectiveness of using hysterectomy for treating HMB?

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

33. What are the indications for, effectiveness of, and cost-effectiveness of removing ovaries during hysterectomy versus not removing?

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

34. What are the competencies required by practitioners who wish to carry out surgical techniques and other interventions for HMB?
35. Competencies for investigations?

Appendix D

Declarations of interest

Anna-Marie 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 declared.

Mary Ann Lumsden: contributions to travel expenses to attend scientific meetings from Wyeth, Novo Nordisk and Organon.

Klim McPherson: no interests declared.

Jane Preston: no interests declared.

David Parkin: non-current interests: research funding to department and for conference attendance by Microsulis plc.

Mark Shapley: no interests declared.

Bridgette York: no interests declared.

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Index

Notes
All entries refer to heavy menstrual bleeding (HMB) unless otherwise noted.
vs denotes comparisons.

Abbreviations used in index subentries

COCs	combined oral contraceptives
GDG	Guideline Development Group
HMB	heavy menstrual bleeding
LNG-IUS	levonorgestrel-releasing intrauterine systems
MBL	menstrual blood loss
MEA	microwave endometrial ablation
RCT	randomised controlled trial
REA	rollerball endometrial ablation
TBEA	thermal balloon endometrial ablation
TCRE	transcervical resection of endometrium

See also the abbreviations listed on page viii.

Other NICE guidelines produced by the National Collaborating Centre for Women's and Children's Health include:

- **Antenatal care: routine care for the healthy pregnant woman**
- **Fertility: assessment and treatment for people with fertility problems**
- **Caesarean section**
- **Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people**
- **Long-acting reversible contraception: the effective and appropriate use of long-acting reversible contraception**
- **Urinary incontinence: the management of urinary incontinence in women**

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- **Diabetes in pregnancy**
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- **Antenatal care (update)**
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Enquiries regarding the above guidelines can be addressed to:

National Collaborating Centre for Women's and Children's Health
27 Sussex Place
Regent's Park
London
NW1 4RG
team@ncc-wch.org.uk

A version of this guideline for the public is available from the NICE website (www.nice.org.uk/CG044publicinfo) or from the NHS Response Line (0870 1555 455); quote reference number N1181.

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