Long-acting reversible contraception

the effective and appropriate use of long-acting reversible contraception

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

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Amber Valley Primary Care Trust
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Ashfield and Mansfield District Primary Care Trust
Association of British Healthcare Industries
Association of Surgeons of Great Britain and Ireland
Association of the British Pharmaceuticals Industry (ABPI)
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Dacorum Primary Care Trust
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Down's Syndrome Association
Ealing Primary Care Trust
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National Institute for Health and Clinical Excellence (NICE)
National Osteoporosis Society
National Patient Safety Agency
National Public Health Service – Wales
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The Royal West Sussex Trust
The Survivors Trust
Trafford Primary Care Trusts
University College London Hospitals NHS Trust
Vale of Aylesbury Primary Care Trust
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Abbreviations

ALOs	*Actinomyces*-like organisms
BMD	bone mineral density
BMI	body mass index
BNF	British National Formulary
BTB	breakthrough bleeding
CHC	combined hormonal contraceptive
CI	confidence interval
COC	combined oral contraceptive
CVD	cardiovascular disease
DFFP	Diploma of the Faculty of Family Planning and Reproductive Health Care
DH	Department of Health
DMPA	depot medroxyprogesterone acetate
*e*MC	Electronic Medicines Compendium
ENG	etonogestrel
FPC	family planning clinic
FFPRHC	Faculty of Family Planning and Reproductive Health Care
GDG	Guideline Development Group
GP	general practitioner
GPP	good practice point
GU	genitourinary
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HTA	Health Technology Assessment
IUS	intrauterine system
ICER	incremental cost effectiveness ratio
IUD	intrauterine device
LARC	long-acting reversible contraception
LDL	low-density lipoprotein
LNG	levonorgestrel
LoC	letter of competence
LSHTM	London School of Hygiene and Tropical Medicine
MBL	menstrual blood loss
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MPA	medroxyprogesterone acetate
NCC-MH	National Collaborating Centre for Mental Health
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NET-EN	norethisterone enantate
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NMC	Nursing and Midwifery Council
NSAID	non-steroidal anti-inflammatory drug
OC	oral contraceptive pill
OR	odds ratio
PCT	primary care trust
PID	pelvic inflammatory disease
POC	progestogen-only oral contraceptive
POICs	progestogen-only injectable contraceptives
POSDIs	progestogen-only subdermal implants

QALY	quality adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RR	risk ratio
SD	standard deviation
SPC	Summary of Product Characteristics
STI	sexually transmitted infection
STIF	sexually transmitted infections foundation course
TTP	time to pregnancy
UKSPR	UK Selected Practice Recommendations for Contraceptive Use
VTE	venous thromboembolism
WHO	World Health Organization
WHO-MEC	World Health Organization Medical Eligibility Criteria for Contraceptive Use
WHOSPR	World Health Organization Selected Practice Recommendations for Contraceptive Use
WMD	weighted mean difference

Glossary of terms

Bias

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

Blinding or masking

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

Case–control study

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

Case report (or case study)

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

Case series

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

Clinical trial

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

Cohort

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

Cohort study

An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus, within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, for example, comparing mortality between one group that received a specific treatment and one group that did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past

records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Confidence interval

A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that is consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which there is 95% confidence that the true effect lies.

Control group

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

Controlled clinical trial

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

Cost effectiveness analysis

A type of economic evaluation where outcomes are expressed in natural units, for example, number of cases cured, number of lives saved, etc.

Crossover study design

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

Cross-sectional study

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

Decision-analytic model

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

Dominance

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

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

Dysmenorrhoea
Painful menstrual bleeding.

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

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

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

Exclusion criteria
See **selection criteria**.

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

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

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

Gillick competence
See **Fraser guidelines**.

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

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

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

Heterogeneity
Or lack of **homogeneity**. The term is used in **meta-analysis** and **systematic review** when the results or estimates of effects of treatment from separate studies seem to be very different, in terms of the size of treatment effects, or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of patient populations, outcome measures, definition of **variables** or duration of follow-up.

Homogeneity
This means that the results of studies included in a **systematic review** or **meta-analysis** are similar and there is no evidence of **heterogeneity**. Results are usually regarded as homogeneous when

	differences between studies could reasonably be expected to occur by chance.
Incidence	The rate of occurrence of new cases of a particular disease in a population being studied.
Inclusion criteria	See **selection criteria**.
Incremental cost effectiveness ratio	A method of presentation of results of an economic evaluation; it expresses the additional (incremental) cost incurred for an additional unit of benefit gained, by adopting an intervention over its comparator.
Intervention	Healthcare action intended to benefit the patient, for example, with drug treatment, surgical procedure or psychological therapy.
Kaplan–Meier method	A nonparametric technique for estimating time-related events (the survivorship function). Ordinarily it is used to analyse death as an outcome. It may be used effectively to analyse time to an endpoint, such as remission.
Level one service	Minimum level of provision within primary care sexual health services.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a **cross-sectional study**, which observes a defined set of people at a single point in time.)
Masking	See **blinding**.
Menarche	The beginning of the menstrual function, particularly the first menstrual period of a female.
Menopause	The period of natural cessation of menstruation, usually occurring between the ages of 45 and 50 years, signalling the end of a woman's reproductive capacity.
Menorrhagia	Excessive or prolonged menstrual bleeding.
Metromenorrhagia	Uterine bleeding between menstrual periods and increased flow of bleeding during menstrual periods.
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, for example, because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also **systematic review** and **heterogeneity**.
Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.
Nulliparity	Having never given birth to a viable infant.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (for example, whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a **confidence interval**) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of one between two

	treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the **relative risk** (which uses actual risks and not odds) will be very similar. See also **relative risk** and **risk ratio**.
Oligomenorrhoea	Reduction in the frequency of menstrual bleeding.
Osteopenia	Decreased calcification or density of bone.
Osteoporosis	A reduction in the amount of bone mass that can lead to fractures after minimal trauma.
Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional, patient and carer representatives.
Perimenopausal	The time leading up to menopause when oestrogen levels begin to drop.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the **control group** in a **clinical trial**, which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants and investigators are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Postpartum	Occuring in or being the period following childbirth.
Power	See **statistical power**.
Premenstrual syndrome	Symptoms manifested by some women prior to menstruation including irritability, insomnia, fatigue, headache and abdominal pain.
Prevalence	The number of cases of disease or other eventualities which occur in a population at or during a given time.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are **retrospective**.
p value	If a study is done to compare two treatments then the p value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the p value was 0.03. What this means is that, if there really was no difference between treatments, there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of p is below 0.05 (that is, less than 5%) the result is seen as statistically significant. Where the value of p is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the **confidence interval**.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, for example, a patient's description of

their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.

Quantitative research

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

Random allocation or randomisation

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

Randomised controlled trial

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

Relative risk

A summary measure which represents the ratio of the risk of a given event or outcome (for example, an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is one. In a study comparing two treatments, a relative risk of two would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment.

Reliability

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

Retrospective study

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

Risk ratio

Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (**control**) **group**.

Sample

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

Screening

The presumptive identification of an unrecognised disease or defect by means of tests, examinations or other procedures that can be applied rapidly. Screening tests differentiate apparently well people who may have a disease from those who probably do not. A screening

	test is not intended to be diagnostic but should be sufficiently sensitive and specific to reduce the proportion of false results, positive or negative, to acceptable levels. People with positive or suspicious findings must be referred to the appropriate healthcare provider for diagnosis and necessary treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity analysis	A technique used in economic evaluation in order to test the robustness of the results under the uncertainty/imprecision in the estimates of costs and outcomes, or under methodological controversy.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two **variables**, given that an association exists. For example, 80% power in a clinical trial means that the study has an 80% chance of ending up with a **p value** of less than 5% in a statistical test (that is, a statistically significant treatment effect) if there really was an important difference (for example, 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also **p value**.
Sterilisation – female	Surgical contraceptive methods, whereby the fallopian tubes undergo bilateral ligation or interruption.
Sterilisation – male	Surgical contraceptive method, whereby the vas deferens undergoes bilateral ligation or interruption.
Systematic review	A review in which evidence from scientific studies is identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a **meta-analysis**.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure.
Variable	A measurement that can vary within a study, for example, the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature that can be assessed or measured.

1. Introduction

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

Included in the category of LARC are the copper intrauterine devices (nonhormonal) and three progestogen-only methods of contraception (intrauterine system, injectables and the implants). The combined vaginal ring is not licensed in the UK and is therefore excluded from this guideline.

In 2003/04, about 8% of women aged 16–49 years in Great Britain used LARC as a method of contraception.[1] [EL = 3]

1.1 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[2] The guideline has been developed with the aim of providing guidance on LARC. The effectiveness of barrier and oral contraceptive pills is dependent on their correct and consistent use. In contrast, long-acting reversible methods have effectiveness that does not depend on daily adherence. Currently there is a very low uptake of LARC (around 8% of contraceptive usage in 2003/04).[1] A number of factors contribute to this. Issues for providers include the initial cost, which may be thought of as too high, particularly if the methods may not be used or required for the intended duration, the need for specific clinical skills (including awareness of current best practice, insertion practice and ability to give information or advice on the methods available) and facilities. Expert clinical opinion is that LARC methods may have a wider role and an increase in their use could help to reduce unintended pregnancy. The current very low uptake suggests that healthcare professionals need better guidance and training so that they can help women to make an informed choice from a full range of contraceptive methods. Enabling women to make an informed choice about LARC and addressing consumer preferences is an important objective of this guideline.

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

1.2 Areas outside the remit of the guideline

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

1.3 For whom is the guideline intended?

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

- professional groups who are involved in the care of women seeking advice on contraception (including general practitioners, gynaecologists, nurses, and practitioners in community contraceptive clinics, sexual health clinics and hospital services)
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health and trust managers
- women seeking advice on contraception, their families and other carers.

A version of this guideline for women seeking contraceptive advice, their families and the public is available, entitled *Long-acting reversible contraception – understanding NICE guidance.* It can be downloaded from the NICE website (www.nice.org.uk/CG030) or ordered via the NHS Response Line (0870 1555 455) and quote reference number NO916.

1.4 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included: two consumers, two general practitioners, two family planning nurses, three specialist family planning doctors and one genitourinary medicine physician.

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

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

1.5 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including *A Strategic Framework for Promoting Sexual Health in Wales* (January 2000),[3] *The National Strategy for Sexual Health and HIV* (in England; July 2001),[4] and the subsequent implementation plan (June 2002).[5] Improving access to contraception, and to the range of methods available as an integral part of broader sexual health services, is an essential element in achieving this aim.

1.6 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in *The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups* (available at www.nice.org.uk/page.aspx?o=201982).[6]

Literature search strategy

The aim of the literature review was to identify and synthesise relevant published evidence. However, evidence submitted by stakeholder organisations was considered and, if relevant to the clinical questions and of equivalent or better quality than evidence identified in the literature searches, was also included. Relevant guidelines produced by other development groups were identified using internet resources, including the National Guideline Clearinghouse, Scottish Intercollegiate Guideline Network (SIGN) and Turning Research into Practice (TRIP). The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Evidence to answer the clinical questions formulated and agreed by the GDG was identified using biomedical databases via the OVID platform. Searches were performed using relevant medical subject headings and free-text terms. No language restrictions were applied to the searches. Both generic and specially developed search filters were employed when necessary. Databases searched were MEDLINE (1966 onwards), EMBASE (1980 onwards), Cochrane Central Register of Controlled Trials (4th Quarter 2004), Cochrane Database of Systematic Reviews (4th Quarter 2004), Database of Abstracts of Review of Effects (4th Quarter 2004), and Cumulative Index to Nursing & Allied Health Literature (1982 onwards). POPLINE®, a specialist reproduction database maintained by Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs, was also utilised.

Searches to identify economic studies were undertaken using the above databases, as well as the Health Economic Evaluations Database and the National Health Service Economic Evaluations Database.

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

A preliminary scrutiny of titles and abstracts was undertaken and full copies of publications that addressed the clinical questions were obtained. Following a critical appraisal of each publication, studies that did not report relevant outcomes or were not relevant to a particular clinical question were excluded.

Searches were rerun at the end of the guideline development process, thereby including evidence published and included in the literature databases up to 1 February 2005. Any evidence published after this date was not considered for inclusion. This date should be considered for the starting point for searching for new evidence for future updates to this guideline.

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

Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[7–13] and classified using the established hierarchical system shown in Table 1.1.[13] This system reflects the susceptibility to bias that is inherent in particular study designs.

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

Table 1.1 Levels of evidence for intervention studies[13]

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

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

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

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

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

Health economics

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

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

The decision-analytic model was developed by the health economists with the support of the GDG, who provided guidance on the data needed to populate the model and on the assumptions required to make appropriate comparisons. Full details on the methodology, the structure of the model and the underlying assumptions, the data used (clinical effectiveness and UK-based cost data), the range of values used in the sensitivity analysis, as well as the full results of the economic analysis are also presented in Chapter 8.

Forming and grading recommendations

For each clinical question, recommendations were derived using, and explicitly linked to, the evidence that supported them. Initially guideline recommendations were based on an informal consensus. Consensus was achieved at formal GDG meetings to finalise the agreement of recommendations and audit criteria.

Each recommendation was graded according to the level of evidence upon which it was based using the established system shown in Table 1.2.[13] For issues of therapy or treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would

Table 1.2 Classification of recommendations[13]

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

equate to a grade A recommendation. For issues of prognosis, the best possible level of evidence (a cohort study) would equate to a grade B recommendation. However, this should not be interpreted as an inferior grade of recommendation because it represents the highest level of relevant evidence. Indirect evidence on contraceptive devices not licensed in the UK was extrapolated to form recommendations reflecting a lower grading.

External review

The guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholders the opportunity to comment on the scope of the guideline 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 two stages of consultation by registered stakeholders and validation by the Institute. After the second consultation, changes were made to the final document. A summary of these changes is presented in Appendix A.

Outcome measures used in the guideline

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

2. Summary of recommendations and practice algorithm

2.1 Summary of recommendations

Chapter 3 Contraceptive use and principles of care

Contraceptive provision

Women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. (Chapter 3.2) — D(GPP)

Women should be provided with the method of contraception that is most acceptable to them provided it is not contraindicated. (Chapter 3.8) — D(GPP)

Contraceptive service providers should be aware that — C

- all currently available LARC methods (intrauterine devices [IUDs], the intrauterine system [IUS], injectable contraceptives and implants) are more cost effective than the combined oral contraceptive pill even at 1 year of use
- IUDs, the IUS and implants are more cost effective than the injectable contraceptives
- increasing the uptake of LARC methods will reduce the number of unintended pregnancies. (Chapter 8.6)

Provision of information and informed choice

Women considering LARC methods should receive detailed information – both verbal and written – that will enable them to choose a method and use it effectively. This information should take into consideration their individual needs and should include: (Chapter 3.5) — D(GPP)

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

Counselling about contraception should be sensitive to cultural differences and religious beliefs. (Chapter 3.5) — D(GPP)

Healthcare professionals should have access to trained interpreters for women who are not English speaking, and to advocates for women with sensory impairments or learning disabilities. (Chapter 3.5) — D(GPP)

Contraceptive prescribing

A medical history – including relevant family, menstrual, contraceptive and sexual history – should be taken as part of the routine assessment of medical eligibility for individual contraceptive methods. (Chapter 3.6) D(GPP)

Healthcare professionals helping women to make contraceptive choices should be familiar with nationally agreed guidance on medical eligibility and recommendations for contraceptive use. (Chapter 3.6) D(GPP)

When considering choice of LARC methods for specific groups of women and women with medical conditions, healthcare professionals should be aware of and discuss with each woman any issues that might affect her choice. (Chapter 3.5/3.6) D(GPP)

Healthcare professionals should exclude pregnancy by taking the menstrual and sexual history before initiating any contraceptive methods. (Chapter 3.6) D(GPP)

Healthcare professionals should supply an interim method of contraception at the first appointment if required. (Chapter 3.6) D(GPP)

Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of LARC is being used outside the terms of the UK Marketing Authorisation. This should be discussed and documented in the notes. (Chapter 3.6) D(GPP)

Women who have a current venous thromboembolism (VTE) and need hormonal contraception while having treatment for the VTE should be referred to a specialist in contraceptive care. (Chapter 5.7) D(GPP)

Contraception and sexually transmitted infection

Healthcare professionals providing contraceptive advice should promote safer sex. (Chapter 3.11) D(GPP)

Healthcare professionals providing contraceptive advice should be able to assess risk for sexually transmitted infections (STIs) and advise testing when appropriate. (Chapter 3.11) D(GPP)

Healthcare professionals should be able to provide information about local services for STI screening, investigation and treatment. (Chapter 3.11) D(GPP)

Contraception for special groups

Healthcare professionals should be aware of the law relating to the provision of advice and contraception for young people and for people with learning disabilities. Child protection issues and the Fraser guidelines should be considered when providing contraception for women younger than 16 years.* (Chapter 3.13) D(GPP)

Women with learning and/or physical disabilities should be supported in making their own decisions about contraception. (Chapter 3.13) D(GPP)

Contraception should be seen in terms of the needs of the individual rather than in terms of relieving the anxieties of carers or relatives. (Chapter 3.13) D(GPP)

When a woman with a learning disability is unable to understand and take responsibility for decisions about contraception, carers and other involved parties should meet to address issues around the woman's contraceptive need and to establish a care plan. (Chapter 3.13) D(GPP)

Training of healthcare professionals in contraceptive care

Healthcare professionals advising women about contraceptive choices should be competent to: (Chapter 3.14) D(GPP)

* See the Department of Health's *Best Practice Guidance for Doctors and Other Health Professionals on the Provision of Advice and Treatment to Young People under 16 on Contraception, Sexual and Reproductive Health* (July 2004), available from www.dh.gov.uk.

- help women to consider and compare the risks and benefits of all methods relevant to their individual needs
- manage common side effects and problems.

Contraceptive service providers who do not provide LARC in their practice or service should have an agreed mechanism in place for referring women for LARC. (Chapter 3.14) D(GPP)

Healthcare professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. (Chapter 3.14) D(GPP)

IUDs and the IUS should only be fitted by trained personnel with continuing experience of inserting at least one IUD or one IUS a month. (Chapter 4.10/5.10) C

Contraceptive implants should be inserted and removed only by healthcare professionals trained in the procedure. (Chapter 7.9) D(GPP)

Chapter 4 Copper intrauterine devices (IUDs)

Decision making

Women should be given the following information.

Contraceptive efficacy

- IUDs act by preventing fertilisation and inhibiting implantation. (Chapter 4.1) C
- The licensed duration of use for IUDs containing 380 mm^2 copper ranges from 5 to 10 years, depending on the type of device. (Chapter 4.1) D
- The pregnancy rate associated with the use of IUDs containing 380 mm^2 copper is very low (fewer than 20 in 1000 over 5 years). (Chapter 4.2) C
- There is no evidence of a delay in the return of fertility following removal or expulsion of IUDs. (Chapter 4.8) C

Effect on periods

- Heavier bleeding and/or dysmenorrhoea are likely with IUD use. (Chapter 4.5) C

Risks and possible side effects

- Up to 50% of women stop using IUDs within 5 years; the most common reasons for discontinuation are unacceptable vaginal bleeding and pain. (Chapter 4.4) C
- There is no evidence that IUD use affects weight. (Chapter 4.6) C
- Any changes in mood and libido are similar whether using IUDs or the IUS, and the changes are small. (Chapter 4.6) C
- The risk of uterine perforation at the time of IUD insertion is very low (less than 1 in 1000). (Chapter 4.7) D
- The risk of developing pelvic inflammatory disease following IUD insertion is very low (less than 1 in 100) in women who are at low risk of STIs. (Chapter 4.7) C
- IUDs may be expelled but this occurs in fewer than 1 in 20 women in 5 years. (Chapter 4.3) C
- The risk of ectopic pregnancy when using IUDs is lower than when using no contraception. (Chapter 4.7) D
- The overall risk of ectopic pregnancy when using the IUD is very low, at about 1 in 1000 in 5 years. C
- If a woman becomes pregnant with the IUD in situ, the risk of ectopic pregnancy is about 1 in 20, and she should seek advice to exclude ectopic pregnancy. (Chapter 4.7) C

Other issues to consider before fitting an IUD

Women who are aged 40 years or older at the time of IUD insertion may retain the device until they no longer require contraception, even if this is beyond the duration of the UK Marketing Authorisation.* (Chapter 4.1) — D

Contraceptive care providers should be aware that the risk of perforation is related to the skill of the healthcare professional inserting the IUD. (Chapter 4.7) — D(GPP)

Testing for the following infections should be undertaken before IUD insertion: (Chapter 4.9) — D(GPP)

- *Chlamydia trachomatis* in women at risk of STIs
- *Neisseria gonorrhoeae* in women from areas where the disease is prevalent and who are at risk of STIs
- any STIs in women who request it.

If testing for STIs is not possible, or has not been completed, prophylactic antibiotics should be given before IUD insertion in women at increased risk of STIs. (Chapter 4.9) — D(GPP)

Women with identified risks associated with uterine or systemic infection should have investigations, and appropriate prophylaxis or treatment before insertion of an IUD. (Chapter 4.9) — D(GPP)

Specific groups, medical conditions and contraindications

IUDs may be used by adolescents, but STI risk should be considered where relevant. (Chapter 4.11) — D(GPP)

Healthcare professionals should be aware that:

- IUD use is not contraindicated in nulliparous women of any age (Chapter 4.11) — D(GPP)
- women of all ages may use IUDs (Chapter 4.11) — D(GPP)
- IUDs can safely be used by women who are breastfeeding. (Chapter 4.11) — C

Healthcare professionals should be aware that: (Chapter 4.12) — D(GPP)

- IUD use is not contraindicated in women with diabetes
- IUD use is a safe and effective method of contraception for women who are HIV-positive or have AIDS (safer sex using condoms should be encouraged in this group).

Practical details of fitting IUDs

The most effective IUDs contain at least 380 mm^2 of copper and have banded copper on the arms. This, together with the licensed duration of use, should be considered when deciding which IUD to use. (Chapter 4.2) — B

Provided that it is reasonably certain that the woman is not pregnant, IUDs may be inserted: (Chapter 4.9) — D(GPP)

- at any time during the menstrual cycle
- immediately after first- or second-trimester abortion, or at any time thereafter
- from 4 weeks postpartum, irrespective of the mode of delivery.

Emergency drugs including anti-epileptic medication should be available at the time of IUD insertion in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation. (Chapter 4.12) — D(GPP)

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

Advice for women at time of fitting

Women should be informed: (Chapter 4.7/4.9/4.3) — D(GPP)

- about symptoms of uterine perforation or infection that would warrant an early review of IUD use
- that insertion of an IUD may cause pain and discomfort for a few hours and light bleeding for a few days, and they should be informed about appropriate pain relief
- about how to check for the presence of IUD threads and encouraged to do this regularly with the aim of recognising expulsion.

Follow-up and managing problems

A follow-up visit should be recommended after the first menses, or 3–6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be strongly encouraged to return at any time to discuss problems, if she wants to change her method of contraception, or if it is time to have the IUD removed. (Chapter 4.14) — D(GPP)

Heavier and/or prolonged bleeding associated with IUD use can be treated with non-steroidal anti-inflammatory drugs and tranexamic acid. (Chapter 4.5) — B

Women who find heavy bleeding associated with IUD use unacceptable may consider changing to a levonorgestrel intrauterine system (LNG-IUS). (Chapter 4.5) — D(GPP)

The presence of *Actinomyces*-like organisms on a cervical smear in a woman with a current IUD requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. (Chapter 4.7) — D(GPP)

Women who have an intrauterine pregnancy with an IUD *in situ* should be advised to have the IUD removed before 12 weeks' completed gestation, whether or not they intend to continue the pregnancy. (Chapter 4.7) — D(GPP)

Chapter 5 Intrauterine system (IUS)

Decision making

Women should be given the following information.

Contraceptive efficacy

- The IUS may act predominantly by preventing implantation and sometimes by preventing fertilisation. (Chapter 5.1) — D(GPP)
- The pregnancy rate associated with the use of the IUS is very low (fewer than 10 in 1000 over 5 years). (Chapter 5.2) — C
- The licensed duration of use for IUS is 5 years for contraception. (Chapter 5.1) — D
- There is no evidence of a delay in the return of fertility following removal or expulsion of the IUS. (Chapter 5.8) — C

Effects on periods

- Irregular bleeding and spotting are common during the first 6 months following IUS insertion. (Chapter 5.5) — C
- Oligomenorrhoea or amenorrhoea is likely by the end of the first year of IUS use. (Chapter 5.5) — C

Risks and possible side effects

- Up to 60% of women stop using the IUS within 5 years. The most common reasons are unacceptable vaginal bleeding and pain; a less common reason is hormonal (non-bleeding) problems. (Chapter 5.4) — C
- There is no evidence that IUS use causes weight gain. (Chapter 5.6) — C

- Any changes in mood and libido are similar whether using the IUS or IUDs, and the changes are small. (Chapter 5.6) — C
- There may be an increased likelihood of developing acne as a result of absorption of progestogen, but few women discontinue IUS use for this reason. (Chapter 5.6) — C
- The risk of uterine perforation at the time of IUS insertion is very low (less than 1 in 1000). (Chapter 5.7) — D
- The risk of developing pelvic inflammatory disease following IUS insertion is very low (less than 1in 100) in women who are at low risk of STIs. (Chapter 5.7) — C
- The IUS may be expelled, but this occurs in fewer than 1 in 20 women in 5 years. (Chapter 5.3) — C
- The risk of ectopic pregnancy when using the IUS is lower than when using no contraception. (Chapter 5.7) — D
- The overall risk of ectopic pregnancy when using the IUS is very low, at about 1 in 1000 in 5 years. (Chapter 5.7) — D(GPP)
- If a woman becomes pregnant with the IUS *in situ*, the risk of ectopic pregnancy is about 1 in 20, and she should seek advice to exclude ectopic pregnancy. (Chapter 5.7) — D(GPP)

Other issues to consider before fitting an IUS

Women who are aged 45 years or older at the time of IUS insertion and who are amenorrhoeic may retain the device until they no longer require contraception, even if this is beyond the duration of UK Marketing Authorisation.* (Chapter 5.1) — D

Contraceptive care providers should be aware that the risk of perforation is related to the skill of the healthcare professional inserting the IUS. (Chapter 5.7) — D(GPP)

Testing for the following infections should be undertaken before IUS insertion: (Chapter 5.9) — D(GPP)

- *Chlamydia trachomatis* in women at risk of STIs
- *Neisseria gonorrhoeae* in women from areas where the disease is prevalent and who are at risk of STIs
- any STIs in women who request it.

If testing for STIs is not possible, or has not been completed, prophylactic antibiotics should be given before IUS insertion in women at increased risks of STIs. (Chapter 5.9) — D(GPP)

Women with identified risks associated with uterine or systemic infection should have investigations, and appropriate prophylaxis or treatment before insertion of the IUS. (Chapter 5.9) — D(GPP)

Specific groups, medical conditions and contraindications

The IUS may be used by adolescents, but STI risk should be considered where appropriate. (Chapter 5.11) — D(GPP)

Healthcare professionals should be aware that:

- IUS use is not contraindicated in nulliparous women of any age. (Chapter 5.11) — D(GPP)
- women of all ages may use the IUS. (Chapter 5.11) — D(GPP)
- the IUS can safely be used by women who are breastfeeding. (Chapter 5.11) — D

* 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.

Healthcare professionals should be aware that:

- there is no evidence that the effectiveness of the IUS is reduced when taking any other medication. (Chapter 5.13) — D
- IUS use is not contraindicated in women with diabetes. (Chapter 5.12) — D(GPP)
- IUS is a safe and effective method of contraception for women who are HIV-positive or have AIDS (safer sex using condoms should be encouraged in this group). (Chapter 5.12) — D(GPP)
- all progestogen-only methods, including the IUS, may be used by women who have migraine with or without aura. (Chapter 5.6) — D(GPP)
- women with a history of venous thromboembolism may use the IUS. (Chapter 5.7) — D(GPP)
- IUS is medically safe for women to use if oestrogen is contraindicated. (Chapter 5.7) — D(GPP)

Practical details of fitting the IUS

Provided that it is reasonably certain that the woman is not pregnant, the IUS may be inserted: (Chapter 5.9) — D(GPP)

- at any time during the menstrual cycle (but if the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be used for the first 7 days after insertion)
- immediately after first- or second-trimester abortion, or at any time thereafter
- from 4 weeks postpartum, irrespective of the mode of delivery.*

Emergency drugs including anti-epileptic medication should be available at the time of IUS insertion in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation. (Chapter 5.12) — D(GPP)

Advice for women at time of fitting

Women should be informed: — D(GPP)

- about symptoms of uterine perforation or infection that would warrant an early review of IUS use (Chapter 5.7)
- that insertion of an IUS may cause pain and discomfort for a few hours and light bleeding for a few days, and they should be informed about appropriate pain relief (Chapter 5.9)
- about how to check for the presence of IUS threads, and encouraged to do this regularly with the aim of recognising expulsion. (Chapter 5.3)

Follow-up and managing problems

A follow-up visit should be recommended after the first menses, or 3–6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be strongly encouraged to return at any time to discuss problems, if she wants to change her method of contraception, or if it is time to have the IUS removed. (Chapter 5.14) — D(GPP)

The presence of *Actinomyces*-like organisms on a cervical smear in a woman with a current IUS requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. (Chapter 5.7) — D(GPP)

* At the time of publication (October 2005), use before 6 weeks postpartum was outside the UK marketing authorisation for the IUS. 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.

Women with an intrauterine pregnancy with an IUS *in situ* should be advised to have the IUS removed before 12 completed weeks of gestation whether or not they intend to continue the pregnancy. (Chapter 5.7) **D(GPP)**

Chapter 6 Progestogen-only injectable contraceptives (POICs)

Decision making

Women should be given the following information.

Contraceptive efficacy

- Progestogen-only injectable contraceptives act primarily by preventing ovulation. (Chapter 6.1) **C**
- The pregnancy rate associated with injectable contraceptives, when given at the recommended intervals, is very low (fewer than 4 in 1000 over 2 years) and the pregnancy rate with depot medroxyprogesterone acetate (DMPA) is lower than that with norethisterone enantate (NET-EN). (Chapter 6.2) **C**
- DMPA should be repeated every 12 weeks and NET-EN every 8 weeks.* (Chapter 6.1) **C**
- There could be a delay of up to 1 year in the return of fertility after stopping the use of injectable contraceptives. (Chapter 6.7) **C**
- If a woman stops using injectable contraceptives but does not wish to conceive, she should start using a different contraceptive method immediately even if amenorrhoea persists. (Chapter 6.7) **D(GPP)**

Effects on periods

- Amenorrhoea is likely during use of injectable contraceptives; this is more likely with DMPA than NET-EN, is more likely as time goes by, and is not harmful. (Chapter 6.4) **C**
- up to 50% of women stop using DMPA by 1 year; the most common reason for discontinuation is an altered bleeding pattern, including persistent bleeding. (Chapter 6.3) **C**

Risks and possible side effects

- DMPA use may be associated with an increase of up to 2–3 kg in weight over 1 year. (Chapter 6.5) **C**
- DMPA use is not associated with acne, depression or headaches. (Chapter 6.5) **C**
- DMPA use is associated with a small loss of bone mineral density, which is largely recovered when DMPA is discontinued. (Chapter 6.6) **B**
- There is no evidence that DMPA use increases the risk of fracture. (Chapter 6.6) **B**

Other issues to consider before giving injectable contraceptives

Specific groups, medical conditions and contraindications

Because of the possible effect on bone mineral density, care should be taken in recommending DMPA to:

- adolescents, but it may be given if other methods are not suitable or acceptable.† (Chapter 6.6)

* At the time of publication (October 2005), NET-EN was not licensed for long-term use. 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.

† Refer to CSM advice issued in November 2004. Go to www.mrha.gov.uk and search for Depo Provera.

- women older than 40 years, but in general the benefits outweigh the risks, and it may be given if other methods are not suitable or acceptable.* (Chapter 6.6) **D(GPP)**

Healthcare professionals should be aware that:

- women with a body mass index over 30 can safely use DMPA and NET-EN (Chapter 6.10) **D(GPP)**
- women who are breastfeeding can consider using injectable contraceptives. (Chapter 6.10) **C**

Healthcare professionals should be aware that: **D(GPP)**

- all progestogen only-methods, including injectable contraceptives, may be used by women who have migraine with or without aura (Chapter 6.5)
- DMPA is medically safe for women to use if oestrogen is contraindicated (Chapter 6.6)
- injectable contraceptives are not contraindicated in women with diabetes (Chapter 6.11)
- DMPA use may be associated with a reduction in the frequency of seizures in women with epilepsy (Chapter 6.11)
- there is no evidence that DMPA use increases the risk of STI or HIV acquisition (Chapter 6.11)
- DMPA is a safe and effective method of contraception for women with STIs, including HIV/AIDS (safer sex using condoms should be encouraged in this group) (Chapter 6.11)
- women taking liver enzyme-inducing medication may use DMPA and the dose interval does not need to be reduced. (Chapter 6.12)

Practical details of giving injectable contraceptives

Injectable contraceptives should be given by deep intramuscular injection into the gluteal or deltoid muscle or the lateral thigh. (Chapter 6.8) **D(GPP)**

Provided that it is reasonably certain that the woman is not pregnant, the use of injectable contraceptives may be started: (Chapter 6.8) **D(GPP)**

- up to and including the fifth day of the menstrual cycle without the need for additional contraceptive protection
- at any other time in the menstrual cycle, but additional barrier contraception should be used for the first 7 days after the injection
- immediately after first- or second-trimester abortion, or at any time thereafter
- at any time postpartum.

Follow-up and managing problems

Women attending up to 2 weeks late for repeat injection of DMPA may be given the injection without the need for additional contraceptives.† (Chapter 6.8) **D(GPP)**

A pattern of persistent bleeding associated with DMPA use can be treated with mefenamic acid or ethinylestradiol. (Chapter 6.4) **C**

Women who wish to continue DMPA use beyond 2 years should have their individual clinical situations reviewed, the balance between the benefits and potential risks discussed, and be supported in their choice of whether or not to continue.* (Chapter 6.6) **D(GPP)**

* Refer to CSM advice issued in November 2004. Go to www.mhra.gov.uk and search for Depo Provera

† At the time of publication (October 2005), this use was outside the UK marketing authorisation. 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.

Healthcare professionals should be aware that if pregnancy occurs during DMPA use there is no evidence of congenital malformation to the fetus. (Chapter 6.6) D(GPP)

Chapter 7 Progestogen-only subdermal implants (POSDIs)

Decision making

Women should be given the following information.

Contraceptive efficacy

- Implanon® acts by preventing ovulation. (Chapter 7.1) C
- The pregnancy rate associated with the use of Implanon is very low (fewer than 1 in 1000 over 3 years). (Chapter 7.2) C
- Implanon has UK Marketing Authorisation for use for 3 years. (Chapter 7.1) D
- There is no evidence of a delay in the return of fertility following removal of contraceptive implants. (Chapter 7.7) C

Effects on periods

- Bleeding patterns are likely to change while using Implanon. (Chapter 7.4) C
- 20% of women will have no bleeding, while almost 50% of women will have infrequent, frequent or prolonged bleeding. (Chapter 7.4)
- Bleeding patterns are likely to remain irregular over time. (Chapter 7.4)
- Dysmenorrhoea may be reduced during the use of Implanon. (Chapter 7.4)

Risks and possible side effects

- up to 43% of women stop using Implanon within 3 years; 33% of women stop because of irregular bleeding and less than 10% of women stop for other reasons including hormonal (non-bleeding) problems. (Chapter 7.3) C
- Implanon use is not associated with changes in weight, mood, libido or headaches. (Chapter 7.5- 7.5/7.5)
- Implanon use may be associated with acne. (Chapter 7.5)

Other issues to consider before fitting an implant

Specific groups, medical conditions and contraindications

Healthcare professionals should be aware that:

- there is no evidence that the effectiveness or adverse effects of implants vary with the age of the user (Chapter 7.10) C
- women over 70 kg can use Implanon as an effective method of contraception (Chapter 7.10) D(GPP)
- contraceptive implants can safely be used by women who are breastfeeding. (Chapter 7.10) C

Healthcare professionals should be aware that:

- Implanon use is not contraindicated in women with diabetes (Chapter 7.11) D(GPP)
- there is no evidence that implant use increases the risk of STI or HIV acquisition (Chapter 7.11) D(GPP)
- contraceptive implants are a safe and effective method of contraception for women with STI, including HIV/AIDS (safer sex using condoms should be encouraged in this group) (Chapter 7.11) D(GPP)
- all progestogen-only methods, including contraceptive implants, may be used by women who have migraine with or without aura (Chapter 7.5) D(GPP)

- contraceptive implants are medically safe for women to use if oestrogen is contra-indicated (Chapter 7.6) — C
- there is no evidence of an effect of Implanon use on bone mineral density. (Chapter 7.6) — C
- Implanon is not recommended as a contraceptive method for women taking liver enzyme-inducing drugs. (Chapter 7.12) — D

Practical details of fitting implants

Provided that it is reasonably certain that the woman is not pregnant, Implanon may be inserted: (Chapter 7.8) — D(GPP)

- at any time (but if the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be used for first 7 days after insertion)
- immediately after abortion in any trimester
- at any time postpartum.

Advice for women at time of fitting

Women should be informed that Implanon insertion and removal both cause some discomfort and bruising but that technical problems are unusual (less than 1 in 100). (Chapter 7.8) — C

Follow-up and managing problems

No routine follow-up is needed after implant insertion. However, a woman should be strongly encouraged to return at any time to discuss problems, if she wants to change her method of contraception, or if it is time to have the implant removed. (Chapter 7.13) — D(GPP)

Irregular bleeding associated with implant use can be treated with mefenamic acid or ethinylestradiol.* (Chapter 7.4) — B

There is no evidence of a teratogenic effect of Implanon use but, if a woman becomes pregnant and continues with the pregnancy, the implant should be removed. (Chapter 7.6) — D(GPP)

If an Implanon implant cannot be palpated (due to deep insertion, failed insertion or migration) it should be localised by ultrasound investigation before being removed. Deeply inserted implants often need to be removed by an expert. (Chapter 7.8) — D(GPP)

2.2 Future research recommendations

The scarcity of robust evidence to answer important clinical questions on the use of LARC methods by women in the UK has posed great challenges to the developers of this guideline. In the majority of cases, the guideline recommendations are based on extrapolated evidence that is indirect or of poor methodological quality. The GDG has made the following recommendations for research on the basis of its review of the evidence. The GDG regards these questions as being the most important research areas in terms of improving NICE guidance on the use of LARC, and the care of women choosing LARC, when this guideline is updated in 4 years' time.

In making these recommendations for research, the guideline developers consider it important and relevant that the research should be specific to the UK population because there are cultural differences in the response to side effects and non-contraceptive effects of hormonal contraceptives. In addition, freedom to choose any contraceptive method and the provision of a free

* The recommendation on treating irregular bleeding after insertion of a contraceptive implant has been changed (this is recommendation 1.5.4.2 in the NICE guideline). Although the evidence does show that mifepristone is effective at controlling irregular bleeding associated with implants, it is not licensed for this indication. The revised recommendation reads: 'Irregular bleeding associated with implant use can be treated with mefenamic acid or ethinylestradiol.'

contraceptive health service in the UK can influence important outcomes such as continuation rates and patterns of method switching.

Typical use of contraception

Few women use contraception perfectly (that is, exactly in accordance with the product instructions) and consistently. Pregnancy rates during typical use reflect effectiveness of a method among women who use the methods incorrectly or inconsistently. Few data are available on typical use of any contraceptive method among women in the UK. Much of the data on contraceptive effectiveness used in the guideline comes from clinical trials or surveys undertaken in other countries such as the USA. Large prospective cohort studies are required to compare the contraceptive effectiveness of LARC methods with non-LARC methods during typical use in the UK.

Patterns of LARC use

Most women will need to use contraception for more than 30 years. Patterns of contraceptive use vary with age, ethnicity, marital status, fertility intention, education and lifestyle. Large prospective cohort studies are required to identify:

- patterns of use (initiation, continuation and switching between methods) of LARC methods compared with non-LARC methods
- factors which influence the patterns of use of LARC.

Uptake and acceptance of LARC

In addition to individual circumstances and needs, a woman's choice and acceptance of LARC may be influenced by potential health disbenefits (side effects and risks) as well as non-contraceptive benefits (such as alleviation of menorrhagia) of LARC. Large population studies of appropriate design are required to determine these effects on the uptake of LARC methods and the implications for NHS resources.

Bone mineral density in women using DMPA

The effect of injectable contraceptives on bone mineral density in women who have used depot medroxyprogesterone acetate (DMPA) for longer than two years is uncertain. Adequately powered surveys or cross-sectional studies are required to examine the recovery of bone mineral density following discontinuation of DMPA after long-term and very long-term use. Studies are also required to examine the risk of bone fractures in older women.

2.3 LARC selection algorithm

Effective and appropriate use of long-acting reversible contraception

LARC is more cost effective than the combined oral contraceptive pill, even at 1 year of use

Intrauterine devices (IUDs) with at least 380 mm² copper and banded copper on the arms should be considered first-line

- Failure: < 20 in 1000 women over 5 years (if fails, exclude ectopic)
- Ectopic pregnancy: < 1 in 1000 pregnancies (< 1 in 20 of failures)
- Expulsion: < 1 in 20 women over 5 years
- Discontinuation: up to 50% at 5 years
- Nonhormonal method
- Licensed: 5 to 10 years (varies between devices)
- Women aged over 40 years may retain the IUD until they no longer require contraception
- Heavy/longer menstrual periods: can be treated with non-steroidal anti-inflammatory drugs (NSAIDs) or tranexamic acid
- If heavy bleeding is unacceptable, advise switching to IUS
- No delay in return to fertility on discontinuation

Intrauterine systems (IUS) Mirena®

- Failure: < 10 in 1000 women over 5 years (If fails, exclude ectopic)
- Ectopic pregnancy: < 1 in 1000 pregnancies (< 1 in 20 of failures)
- Expulsion: < 1 in 20 women over 5 years
- Discontinuation: up to 60% at 5 years
- Hormonal method
- Licensed: 5 years
- Women aged over 45 years may retain the IUS until they no longer require contraception
- Spotting common in first 6 months
- Oligo/amenorrhoea likely by 1 year
- May be associated with acne
- No delay in return to fertility on discontinuation

Progestogen-only injectable contraceptive (POIC) Depo-Provera® (DMPA)

- Failure: < 4 in 1000 women over 2 years
- Discontinuation: up to 50% at 1 year
- Hormonal method
- Licensed: 12-week dose interval
- Oligo/amenorrhoea likely
- Small reversible reduction in bone mineral density may occur during use
- Weight gain may occur
- Delay in return to fertility of up to 1 year on discontinuation

Progestogen-only subdermal implants (POSDI) Implanon®

- Failure: < 1 in 1000 women over 3 years
- Discontinuation: up to 43% at 3 years
- Hormonal method
- Licensed: 3 years
- Irregular bleeding patterns can occur throughout use: can be treated with mefenamic acid or ethinylestradiol
- No delay in return to fertility on discontinuation

Women of reproductive age requesting contraception, including long-acting reversible contraception (LARC)

Principles of care
Women should be given evidence-based information and offered a choice of all methods of contraception, tailored to their needs, including LARC

Information (verbal and written)
- Failure rate
- Mode/duration of action
- Side effects/risks
- Benefits
- Use of method
- When to seek specific advice
- Safer sex

Assessment
- Medical, family, reproductive, sexual and contraceptive history
- To identify contraindications

Choice
(supply interim method at first appointment if required)

Initiation of method
- By trained healthcare professionals on site or by local referral
- Exclude pregnancy by menstrual and sexual history

Routine follow-up
- **Intrauterine devices/systems**
  3–6 weeks (to check threads and exclude perforation)
  Return if time for removal, otherwise no further follow-up necessary
- **Progestogen-only injectable contraceptive**
  Every 12 weeks for repeat injection of DMPA and every 8 weeks for NET-EN
- **Progestogen-only subdermal implants**
  Return if time for removal, otherwise no further follow-up necessary

Additional follow-up
- Women should be encouraged to return if problems occur, or for reassurance

Investigation and management of problems
- By trained professionals

Adolescents
- IUDs, IUS, implants: no contraindications to use
- DMPA: only if other LARC methods unacceptable; regular review if use longer than 2 years
- Safer sex
- Fraser guidelines if < 16 years
- consider child protection

Women aged over 40 years
- IUDs, IUS, implants: no contraindications to use
- DMPA: regular review if use longer than 2 years

Nulliparity
- All LARC methods: no contraindications to use

HIV/AIDS
- All LARC methods: no contraindications to use
- Safer sex

At risk of STI
- Tests for STIs may be needed before IUD/IUS insertion
- Safer sex

Postpartum
- IUD/IUS insertion from 4 weeks after childbirth
- DMPA: any time after childbirth
- Implants: any time after childbirth

Breastfeeding
- All LARC methods: no contraindications to use

After abortion
- All LARC methods: any time at or following abortion

Diabetes
- All LARC methods: no contraindications to use

Epilepsy
- All LARC methods: no contraindications to use
- Anti-epileptic drugs and emergency drugs available at time of IUD/IUS initiation

Body mass index > 30
- All LARC methods: no contraindications to use

Learning disabilities
- All LARC methods: no contraindications to use
- Information in appropriate format
- Advocates: support in decision making
- Consider consent issues

Physical disabilities
- All LARC methods: no contraindications to use
- Support in decision making

Non-English speaking
- All LARC methods: no contraindications to use
- Information in appropriate format
- Trained interpreter

This algorithm should, when necessary, be interpreted with reference to the full guideline

3. Contraceptive use and principles of care

3.1 Normal fertility

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

In the general population it is estimated that 84% of women would conceive within 1 year of regular unprotected sexual intercourse. This rises cumulatively to 92% after 2 years and 93% after 3 years.[20,21]

The conception rate per menstrual cycle is known as fecundability. Natural female fertility declines with age.[22] [EL = 3] The decline with age in rates of conception is seen after 30 years of age and is more marked after age 35 years.[23,24] [EL = 3]

3.2 Contraceptive provision

In 1994 at the International Conference on Population and Development (ICPD) in Cairo, Egypt, government delegations from 179 countries, including the UK, agreed a Programme of Action to stabilise the world's population. The Programme of Action defined reproductive rights and stated that people should have the freedom to decide if, when, and how often to have children. ICPD further called for universal access to a full range of high-quality, affordable, accessible and convenient sexual and reproductive health services.[25]

Since 1974 contraception has been provided free of prescription charges in the UK. It is provided by general practitioners (GPs), community (NHS) family planning clinics (FPCs) and, increasingly, in some not-for-profit charitable clinics such as Brook (usually limited to young people under 25 years). Contraception is also provided in sexual health clinics, NHS walk-in centres and some genitourinary medicine clinics. Some pharmacies provide emergency contraception free through specific NHS protocols. In Great Britain in 2003/04 almost 57% of women aged 16–49 years had used at least one service in the previous 5 years.[1] Most (81%) had visited their GP surgery but 32% had used a community FPC. Not all settings provide all methods of contraception, and not all doctors are competent to fit intrauterine devices (IUDs) or systems (IUS) or contraceptive implants (refer to Medical Foundation for AIDS and Sexual Health (MedFASH) Sexual Health Standards at www.medfash.org.uk/). Women attending FPCs are more

likely to use a long-acting method of contraception, particularly implants and IUD/IUS, than those consulting their GP.

In the UK, because contraceptives are provided free of charge, cost plays no part in determining an individual's choice of method and does not influence continuation rates or method switching. In countries where contraceptives are not free and where the consultation and procedure may also be charged to the user, cost plays a much bigger part in uptake and continuation and data from these countries must be extrapolated to the UK with caution. In one state in the USA in the early 1990s women were offered a payment of $500 if they had Norplant® inserted and further annual payments of $50 for each year they kept it.[26] Cost, however, is relevant to the service provider and may determine the choice of methods available in some settings. Some local formulary committees withhold approval of the newer, more expensive contraceptive methods (such as the contraceptive patch and newer brands of oral contraceptive pill) arguing that there is no evidence of superiority over existing cheaper methods. Providers' attitudes towards, knowledge of, and preferences for particular methods of contraception influence the choices made by the users.[27] If women/couples are not informed about all available methods of contraception, their choices are restricted.

RECOMMENDATION

Women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception (LARC) methods. **D(GPP)**

3.3 Contraceptive prevalence

Almost everyone in the UK uses contraception at some time in their lives. Contraceptive prevalence has increased dramatically in the last 30 years. In Great Britain in 2003/04, 52% of all women aged 16–49 years were using a reversible method of contraception and just under a quarter had either been sterilised (11%) or had a partner who was sterilised (12%).[1] Of women 'at risk' of pregnancy (i.e. in a heterosexual relationship, presumed fertile and not actively trying to become pregnant) only 2% were not using any method of contraception.[1]

The pattern of contraceptive use varies with age, ethnicity and race, marital status, fertility intentions and education.[28] In Great Britain in 2003/04, the oral contraceptive pill was the most popular method of contraception among women aged 16–49 years (25% of women use it) while the next most popular method was the male condom (23% of women)[1] (Table 3.1). Long-acting methods of contraception (injectables, implants, IUDs and IUS) were used by 8% of women. In general, the IUD/IUS tends to be adopted by older, parous women while injectable contraceptives such as Depo-Provera® and contraceptive implants such as Implanon® are more commonly used by younger women and women without children. Most hormonal methods of contraception have an effect on vaginal bleeding patterns.[29] For women with certain religious beliefs, methods which cause irregular bleeding can be a major inconvenience. Not all methods are available in all countries and not all available methods are marketed in the UK. Women coming to the UK from elsewhere may be using a method which is unavailable or (e.g. norethisterone enantate, NET-EN) only licensed for short-term use in the UK.

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

Unintended pregnancy

Despite the widespread use of contraception, unintended pregnancy is common. In England and Wales the abortion rate for the quarter January–March 2004 was 18.6 per 1000 women of reproductive age. The abortion rates were 33.6 per 1000 for women in the 20–24 year age group, 28.1 per 1000 women for women in the 16–19 years age group and 3.9 per 1000 women in women under 16 years of age.[32] [EL = 3] Not all unintended pregnancies end in abortion. It has been suggested that as many as 30% of pregnancies which end in childbirth are unplanned when they are conceived.[33] A UK questionnaire survey of pregnant women (n = 12 106) designed to investigate the association of duration of OC usage with time to conception reported that

Table 3.1 Current use of contraception by age in Great Britain (women aged 16–49 years); data from the Office for National Statistics

Current use of contraception	Use by each age range (%)								Use by all ages the during the indicated period (%)						
	16 –17	18 –19	20 –24	25 –29	30 –34	35 –39	40 –44	45 –49	2003/ 04	2002/ 03	2001/ 02	2000/ 01	1999/ 2000	1998/ 99	1997/ 98
Nonsurgical															
Pills[a]	26	58	49	40	31	15	12	5	25	25	28	25	26	26	26
Minipill	1	14	9	6	4	4	5	2	5	5	5	5	5	5	5
Combined pill	20	29	31	31	24	10	6	2	17	18	21	17	18	19	19
Male condom	33	36	37	24	24	22	15	14	23	20	21	21	23	21	21
Withdrawal	3	–	1	3	5	5	1	1	3	3	4	3	5	6	4
IUD	2	–	1	3	5	5	5	4	4	5	3	5	4	4	4
Injection/implant	3	2	6	5	4	3	1	1	3	3	3	3	3	2	
Safe period/rhythm method/Persona	–	–	1	1	2	1	1	0	1	1	2	1	2	2	2
Cap/diaphragm	–	1	0	0	1	1	1	2	1	1	1	1	1	1	2
Foam/gels	–	–	–	–	0	0	–	1	0	0	0	0	0	1	0
Hormonal IUS	–	–	0	1	1	1	1	1	1	1	1	1	1	0	0
Female condom	–	–	–	–	0	0	–	–	0	0	0	0	0	0	0
Emergency contraception[b]	5	4	2	0	0	0	–	–	1	1	1	1			
Total using at least one non-surgical method	50	70	75	66	63	48	35	28	52	51	53	51	54	50	52
Surgical															
Sterilised	–	1	2	3	5	17	17	25	11	11	10	11	12	12	11
Partner sterilised	–	–	1	4	9	15	25	20	12	12	12	11	11	12	10
Total using at least one method	50	71	78	73	77	80	77	73	75	74	75	73	76	75	74
Total not using any method	50	29	22	27	23	20	23	27	25	26	25	27	24	25	26

[a] Includes women who did not know the type of pill used.
[b] Category included for the first time in the 2000/01 questionnaire.

29.4% of the pregnancies were unintentional.[34] [EL = 3] Most data suggest that true method failure accounts for fewer than 10% of unintended pregnancies, the rest arising either because no method was used at the time conception occurred (30–50%) or because the method was used inconsistently or incorrectly.[35–37] Failure due to inconsistent use of oral contraception and condoms was reported to be the main cause of pregnancy among women undergoing termination.[38,39] [EL = 3]

It is important for repeat unwanted pregnancies to be prevented rather than aborted. Repeat abortions are common, estimated to be between 27% to 48% of all induced abortions.[40–44] [EL = 3]

Teenage pregnancy

In 2001, 7.4% of all births in England and Wales were to women aged under 20.[45] [EL = 3] In 2003, the under-18 years conception rate was 42.3 per 1000 women (aged 15–17 years) and 46% of these conceptions resulted in legal abortions. In 2002, the under-16 conception rate was 7.9 per 1000 women (aged 13–15 years) and 55.7% of these conceptions led to abortions.[46] [EL = 3] In 2003, the age-standardised abortion rate was 17.5 per 1000 resident women aged 15–44 years (17.0 in 2002). The abortion rate was the highest at 31.4 per 1000, for women in the 20–24 year age group (30.7 in 2002). The under-16 years abortion rate was 3.9 in 2003 compared with 3.7 per 1000 in 2002. Infant mortality rates for children born to teenage mothers are 1.3-fold higher than that for total births, due mainly to low birth weight and congenital anomalies.[47] [EL = 3]

Based on a report by the Social Exclusion Unit (SEU) on teenage pregnancy in 1999,[48] the Department of Health has developed a national strategy to:

- reduce the rate of teenage conceptions, with the specific aim of halving the rate of conceptions among under-18s by 2010, with an interim reduction of 15% by 2004
- set a firmly established downward trend in the under-16 years conception rate by 2010
- increase the participation of teenage parents in education and work, to reduce their risk of long-term social exclusion.[49] [EL = 4]

3.4 Efficacy and effectiveness of contraception

The effectiveness of a method of contraception is judged by the failure rates associated with its use. Table 3.2 shows failure rates for typical use of methods currently available in the USA.[50] The rates are estimated from US studies, including the National Survey of Family Growth, and show the percentage of couples who experience an accidental pregnancy during the first year of use of each method.[51] Similarly collected data are not available for effectiveness of contraceptives in UK use. Effectiveness rates for LARC from a variety of sources are shown in the individual method chapters in this guideline. The effectiveness of a contraceptive depends on its mode of action and how easy it is to use.[52] Pregnancy rates during perfect use of a method reflect its efficacy. If a method prevents ovulation in every cycle in every woman, it should have an efficacy of 100%, since if there is no egg there can be no conception. Only if a mistake is made, or if the method is used inconsistently, will a pregnancy occur. Imperfect use with long-acting methods of contraception is usually due to provider error – undetected uterine perforation during IUD insertion, for example.

The contraceptive implant Implanon® inhibits ovulation for 3 years and is extremely effective as the user has to take no action once the implant is inserted.[53] The combined pill is probably as effective at preventing ovulation and pregnancy; failure rates for perfect use are only 0.1 in 100 within the first year of use. True pill failures are due to incomplete inhibition of ovulation mainly among women who metabolise the pill rapidly. Inhibition of ovulation, however, depends on the pill being taken perfectly. With imperfect use ovulation can occur and typical-use failure rates are 8 in 100 within the first year of use (Table 3.2).[50]

LARC methods are more effective than barrier methods or oral contraceptives because they demand much less – or are independent of the need for – adherence. Failure rates associated with typical use are virtually the same as those associated with perfect use. Active steps must be taken if a woman wishes to stop using an IUD, IUS or implant while discontinuation of other

Table 3.2 Percentage of women experiencing an unintended pregnancy during the first year of typical use, and the first year of perfect use of contraception (United States); adapted with permission from Trussell[435]

Method	Women experiencing an unintended pregnancy within the first year of use (%)	
	Typical use[a]	Perfect use[b]
No method[c]	85	85
Spermicides[d]	29	15
Withdrawal	27	4
Periodic abstinence	25	
Calendar		9
Ovulation method		3
Sympto-thermal[e]		2
Post-ovulation		1
Cap[f]		
Parous women	32	26
Nulliparous women	16	9
Sponge		
Parous women	32	20
Nulliparous women	16	9
Diaphragm[f]	16	6
Condom[g]		
Female (Reality)	21	5
Male	15	2
Combined pill and minipill	8	0.3
Evra patch	8	0.3
NuvaRing	8	0.3
Depo-Provera	3	0.3
Lunelle	3	0.05
IUD		
Progestasert (progesterone T)	2	1.5
ParaGard (copper T)	0.8	0.6
Mirena (LNG-IUS)	0.1	0.1
Norplant and Norplant-2	0.05	0.05
Female sterilisation	0.5	0.5
Male sterilisation	0.15	0.10

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

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

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

[d] Foams, creams, gels, vaginal suppositories and vaginal film.

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

[f] With spermicidal cream or jelly.

[g] Without spermicides.

NB. Some of the methods listed in this table are not available in the UK and some of the methods available in the UK are not available in the USA and therefore are not listed here. This table does not include any data on Implanon. ParaGard® is the TCu 380A IUD.

methods (including injectables) is passive. In a cohort study of US teenagers using Norplant (n = 200), pills (n = 100) or condoms (n = 99), there were no pregnancies among Norplant users while one-third of teenagers using pills or condoms had conceived.[54]

Pregnancy rates are still often described by the Pearl Index (PI) – the number of unintended pregnancies divided by the number of women-years of exposure to the risk of pregnancy while using the method. The PI is expressed as the pregnancy rate per 100 woman-years (a woman-year is defined as 13 menstrual cycles).[55] If, out of 100 women using a contraceptive method for 13 cycles, one becomes pregnant the PI is 1.0.

Failure rates of most methods decrease with time since women most prone to failure will become pregnant soon after starting a method.[51] Over time, a cohort of couples still using a method increasingly comprises couples in which the woman is unlikely to become pregnant (because they are good at using the method, highly motivated to avoid pregnancy, or are infertile). So, the longer a contraceptive trial lasts, the lower the pregnancy rate is likely to be. Furthermore, failure rates in most clinical trials are often underestimated because all of the months of use of the method are taken into account when calculating failure rates, regardless of whether or not intercourse has occurred during that cycle. For long-acting methods of contraception such as IUDs and implants, the pregnancy rate with time (cumulative pregnancy rate) is more informative and is presented as the standard measure of contraceptive effectiveness in this guideline.

The effectiveness of all methods of contraception is likely to be higher in clinical trials than in real life[56] since trial participants are not representative of the general population of contraceptive users and the routine daily recording of contraceptive use (mandatory in trials) enhances adherence. Randomised placebo-controlled trials are widely regarded as the gold standard for determining effectiveness of drugs and other therapeutic interventions. However, use of a placebo is unethical in trials of a contraceptive method since all contraceptive users wish to avoid pregnancy. While RCTs between like methods (one type of copper IUD versus another, or one brand of combined pill versus another) are possible, it is extremely difficult to recruit people willing to participate in RCTs comparing different types of contraceptive. In developed countries most women are well informed about contraceptive choice and have strong views about methods they do – and particularly do not – want to use.[57,58]

The effectiveness of some hormonal methods of contraception is affected by the body weight of the user. Women of a high body weight have higher failure rates with pills,[59] Norplant[60,61] and patches.[62] Body weight may also influence bleeding patterns; women with a low body weight are more likely to experience amenorrhoea while using Norplant.[63] Trials of effectiveness in populations of women with a much lower body weight than that of the average UK female population (such as women from Thailand or Indonesia) may underestimate failure rates and the side effects profile.

3.5 Provision of information and informed choice

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

A UK questionnaire survey of family planning physicians at six centres on counselling Norplant users (n = 521) reported that patient counselling contributed to increasing patient acceptance of

Norplant. Eighty-two percent of women accepted the implants despite an overall rate of menstrual bleeding irregularities of 13%. Pre-insertion counselling occurred 100% of the time at these centres and physicians and nurses were responsible for counselling 78% and 39% of the time, respectively.[65] [EL = 3]

Knowledge and concerns about contraceptive methods

Using a series of semi-structured focus groups, a UK study assessed women's knowledge of the effectiveness of various contraceptive methods and of the risks of thrombosis associated with hormonal contraceptives. Women (n = 45) tended to underestimate the effectiveness of hormonal contraceptives, particularly implants, and to overestimate the risk of thrombosis associated with hormonal contraceptives.[66] [EL = 3] Many were more concerned about the adverse effects (especially bleeding irregularities and weight gain) than about effectiveness.

A US questionnaire survey (n = 249, aged 12–20 years) reported that knowledge of Norplant among the general adolescent population was poor. However, young women who were using Norplant were 11 times more likely than those using other types of contraceptive methods to be more knowledgeable about Norplant, having received additional counselling from healthcare providers.[67] [EL = 3]

Source of information

An audit in the UK undertaken to develop informational materials about new contraceptive products reported that women received information about a broad range of contraception available, but that 33% of women came with their 'own agenda' and were sure before the visit about which method they wanted.[57] [EL = 3]

One survey (n = 4500) in the Netherlands reported that women were well informed about all aspects of contraception as a result of formal and informal education at school, from their families, and by the media. Most of these women (86%) viewed their contraceptive choices as their own. The GP was regarded as the most important and reliable source of information (73%).[58] [EL = 3]

Effect of information on satisfaction and continuation

A Finnish survey of LNG-IUS users (n = 17 360) evaluated the impact of advance information on user satisfaction with the method. User satisfaction was associated with information (on menstrual disturbances, pelvic inflammatory disease (PID), greasiness of hair or skin, and the possibility of pregnancy) given at the time the LNG-IUS was inserted. Women who received information about the possibility of amenorrhoea were more satisfied when compared with the women who were less well informed (OR 5.0, 95% CI 4.1 to 5.9).[68] [EL = 3]

A survey of new DMPA users in Bolivia (n = 352) reported that women who received information on the efficacy, side effects and amenorrhoea of DMPA had higher continuation rates than those who did not receive such information. Women advised to return to the clinic if experiencing problems were 2.7 times more likely to continue DMPA at 1 year, and those advised of amenorrhoea were 2.5 times more likely to return for a second injection of DMPA compared with women who did not receive such information from the provider.[69] [EL = 3] Similar findings were reported from a study of 350 new DMPA users in Mexico where detailed, structured, pre-treatment counselling resulted in fewer method discontinuations at 12 months compared with routine contraceptive counselling (15% versus 39% overall and 9 % versus 32% for menstrual disturbance including amenorrhoea).[70] [EL = 1+]

One RCT (n = 636) in the UK assessed the effectiveness of providing educational leaflets versus verbal information in improving knowledge of contraception in women taking the combined pill. Baseline knowledge of contraception in the control group was poor. Written information had a significant effect on knowledge of factors associated with pill failure. Improvement in knowledge occurred with the provision of summary leaflets (adjusted OR 4.04, 95% CI 1.68 to 9.75), the Family Planning Association's leaflet (OR 3.43, 95%CI 1.45 to 8.09) and asking questions (OR 3.03, 95% CI 1.30 to 7.00). This study suggested that provision of educational leaflets on contraception and/or asking women relevant questions, though time-consuming, may help improve women's knowledge of contraception.[71] [EL = 1+]

Method of information giving

The provision of written information may enhance understanding. One RCT (n = 461) in the USA evaluated three different approaches to increase women's understanding of risk of pregnancy associated with various contraceptive methods. A table with categories of contraceptives communicated relative contraceptive effectiveness better than the tables with numbers. However, without the presentation of the numbers, women grossly overestimated the absolute risk of pregnancy while using contraception. A table, developed by the World Health Organization (WHO), presenting a combination of categories of contraceptives and a general range of risk for each category may provide the most accurate understanding of both relative and absolute pregnancy risk.[72] [EL = 1–]

A survey (n = 211) in the USA reported that women relied heavily on their own experiences in assessing the risks and benefits of oral contraceptives. Written information was cited more frequently than medical personnel as a major source of information on cardiovascular and cancer risks and the benefits of OCs. The internet played a minimal, if any, role in educating women about OCs.[73] [EL = 3]

RECOMMENDATIONS

Women considering LARC methods should receive detailed information – both verbal and written – that will enable them to choose a method and use it effectively. This information should take into consideration their individual needs and should include: D(GPP)

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

Specific groups

One survey (n = 406) in the USA which examined the relationship between reading ability and knowledge of family planning reported that women with low reading skills were 2.2 times more likely to want to know more about birth control methods (95% CI 1.1 to 4.4). They were 4.4 times more likely to have incorrect knowledge about when they were most likely to become pregnant (95% CI 2.1 to 9.0) than women with good reading skills. This raised additional questions of whether women with low reading skills understand the concept of informed consent prior to accepting contraceptive use.[74] [EL = 3]

An interview survey (n = 32) of Somalian women attending a UK well-woman clinic reported that effective contraceptive care and service provision needed to take into account the cultural interpretation of reproduction and family planning within a wider social and religious context in order to meet the needs of these women.[75] [EL = 3]

RECOMMENDATIONS

Counselling about contraception should be sensitive to cultural differences and religious beliefs. D(GPP)

Healthcare professionals should be able to provide information that is in a format appropriate for all women with special needs. D(GPP)

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

Healthcare professionals should have access to trained interpreters for women who are not English speaking, and to advocates for women with sensory impairments or learning disabilities. D(GPP)

3.6 Contraceptive prescribing

Most contraceptive users are medically fit and can use all available methods safely. However, a few medical conditions are associated with theoretical increased health risks with certain contraceptives, either because the method adversely affects the condition (for example, combined hormonal contraceptives may increase the risk of a woman with diabetes developing cardiovascular complications), or because the condition or its treatment affects the contraceptive (some anti-epileptic drugs interfere with the efficacy of hormonal methods). Since most trials of new contraceptive methods deliberately exclude subjects with serious medical conditions, there is little direct evidence on which to base sound prescribing advice. In an attempt to produce a set of international norms for providing contraception to women and men with a range of medical conditions which may contraindicate one or more contraceptive methods, the WHO has developed a system to address medical eligibility criteria for contraceptive use (WHO-MEC).[76] Using evidence-based systematic reviews,[77] the document classifies conditions into one of four categories. Category 1 includes conditions for which there is no restriction for the use of the method while category 4 includes conditions which represent an unacceptable health risk if the contraceptive method is used (absolutely contraindicated). Classification of a condition into category 2 indicates that the method may generally be used but that more careful follow-up is required. Category 3 conditions are those for which the risks of the method generally outweigh the benefits (relatively contraindicated). Provision of a method to a woman with a category 3 condition requires careful clinical judgement since use of that method is not recommended unless there is no acceptable alternative. The WHO-MEC document is available on the internet[63] and a system is in place to incorporate new data into the guidelines as they become available. A UK version of the WHO-MEC document is currently under development by the FFPRHC and will be published by the end of 2005.

In an attempt to provide evidence-based guidance on safe and effective contraception, the WHO produced the *Selected Practice Recommendations for Contraceptive Use* (WHOSPR).[77,78] The UK Selected Practice Recommendations for Contraceptive Use (UKSPR), a document adapted by the FFPRHC for use in the UK, provides guidance on assessment before providing contraceptives, including when to start a method, history taking, follow-up, and the management of common side effects.[79]

The vast majority of women who use hormonal contraception do not have any medical problems and they are young. Providers need to recognise the very few who may be at risk of the rare but serious complications of hormonal contraception. Taking a careful history (including family history) and observing obvious physical characteristics (such as obesity) provides a lot of useful information. The WHO distinguishes between examinations and investigations which are essential for safe prescribing of contraception and those which 'do not contribute substantially to safe and effective use of the contraceptive method' but which are commonly done.[77] Routine breast and pelvic examination, cervical smears and blood tests such as the measurement of serum cholesterol fall into the latter category. The only tests considered mandatory in the UK are the measurement of blood pressure before starting combined hormonal contraception, and pelvic examination before IUD/IUS insertion.

When prescribing contraceptives beyond the duration of product licence, healthcare professionals need to inform the woman and discuss with her the evidence supporting use outside licence, document all this information in case records and obtain her consent.[80] [EL = 1–4]

The UKSPR, in agreement with the WHOSPR, recommends the ideal time in the cycle when a particular method of contraception should be initiated and how best to switch methods. Recognising that this may not always be the most convenient time, the UKSPR further recommends that all methods can be started at any time in the cycle provided it is reasonably certain that the woman is not pregnant. It is not necessary to undertake pregnancy testing before a method is started, even later in the cycle. Pregnancy can be excluded by taking a menstrual and contraceptive history and asking about sexual activity. A test is indicated only if the history suggests that there is a risk that the woman might be pregnant.

RECOMMENDATIONS

A medical history – including relevant family, menstrual, contraceptive and sexual history – should be taken as part of the routine assessment of medical eligibility for individual contraceptive methods. D(GPP)

Healthcare professionals helping women to make contraceptive choices should be familiar with nationally agreed guidance on medical eligibility and recommendations for contraceptive use. D(GPP)

Healthcare professionals should exclude pregnancy by taking the menstrual and sexual history before initiating any contraceptive method. D(GPP)

Healthcare professionals should supply an interim method of contraception at the first appointment if required. D(GPP)

Healthcare professionals should ensure that informed consent is obtained from the woman whenever any method of LARC is being used outside the terms of the UK Marketing Authorisation.* This should be discussed and documented in the notes. D(GPP)

3.7 Health benefits of contraception

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

Most couples use contraception for over 30 years. Additional health benefits beyond pregnancy prevention offer significant advantages and influence acceptability. In a nationwide sample of 943 US women, satisfaction with oral contraception was most likely among women aware of the non-contraceptive benefits of the pill and who experienced few side effects.[69]

Existing combined hormonal methods improve menstrual bleeding patterns, alleviate dysmenorrhoea, acne and sometimes pre-menstrual syndrome and reduce the risk of ovarian and endometrial cancer. Increasing numbers of women choose the LNG-IUS and DMPA because of the amenorrhoea they confer. One non-comparative study (n = 165) in Austria assessed long-term acceptability of LNG-IUS and reported that cessation of menstruation occurred in 47% of women at 3 years, over 80% of whom considered this to be a positive change.[81] [EL = 3] Perimenopausal women appreciate the facility to continue using the LNG-IUS into the menopause when it can be used to deliver the progestogen component of HRT.

The non-contraceptive benefits can influence continuation rates of contraception. One study in the USA demonstrated that women who experienced troublesome dysmenorrhoea prior to using the COC were 8 times more likely to continue using the pill than women who did not report dysmenorrhoea.[82]

3.8 Acceptability

Continuation rates are often regarded as a surrogate for acceptability of a method. This is simplistic. Many factors determine acceptability and continuation of a method may only reflect that it is the best of a bad lot. In recent years clinical trials have routinely included questions on acceptability at regular follow-up intervals but this is at best a crude measure of what is a complex issue. There is evidence to demonstrate that the acceptability of a contraceptive method (and continuation rate) is increased when users are well informed about the side effects and risks.[69]

* Check the Summary of Product Characteristics of individual devices for current licensed indications.

The current uptake of LARC in Great Britain is low (8% of contraceptive usage in 2003/04).[1] In a national survey of 1688 US women (where fewer than 2% used contraceptive implants and under 3% used injectables), women gave three major reasons for not using LARC: lack of knowledge, fear of side effects/risks, and satisfaction with the method they were currently using. Women aged 30 years or older and those with a college education were half as likely as younger women and those without college education to mention fear of side effects as their main reason for not using implants.[83] [EL = 3] Important reasons for choosing a contraceptive included: how well it works,[66,71,72] ease of use and protection against STI and HIV.[72]

Contraceptive choice is strongly influenced by the provider's views and by the advice and information that he/she gives to the potential user. Providers may hold very different views from users. In a study of the acceptability of methods of contraception which confer amenorrhoea,[84] providers thought that having a regular period was important to their clients while women themselves did not feel that it was important. The methods which a provider is able to offer also influence contraceptive choice. If a provider is unable to insert contraceptive implants, he/she is less likely to offer the method or, indeed, to be sufficiently well informed to give good information. Women may settle for a method which is easily available from their GP rather than have to travel to another service to obtain something different.

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

RECOMMENDATION

Women should be provided with the method of contraception that is most acceptable to them provided it is not contraindicated. **D(GPP)**

3.9 Adherence

Many couples use contraception inconsistently and/or incorrectly. Inconsistent or incorrect use accounts for the difference between perfect use and typical use failure rates. Some methods are easier to use than others. The IUD/IUS and implants are inserted and removed by a healthcare professional and are completely independent of adherence for efficacy. Their failure rates are accordingly very low (Table 3.2)[85] and typical and perfect use rates are almost the same. Progestogen-only injectables last 8 to 12 weeks, but still demand the motivation and organisational skills required to attend for repeat doses. Adherence to oral contraception is not easy. In one US study, 47% of women reported missing one or more pills per cycle and 22% reported missing two or more pills per cycle.[27] In a study using electronic diaries to record adherence, 63% of women missed one or more pills in the first cycle of use, and 74% in the second cycle.[52] Typical use failure rates are even higher with methods of contraception (condoms, diaphragms, withdrawal and natural family planning) which rely on correct use with every act of intercourse.

A descriptive review assessed the impact of health concerns on adherence to hormonal contraceptives. It reported that contraceptive-related knowledge among sexually active adolescents was poor and the general public had many concerns about the safety of hormonal contraception. The development of side effects, especially those related to menstruation, caused adolescents and young women to feel that their general and reproductive health was being threatened. Counselling tailored to address specific reasons for non-adherence in this population may be beneficial.[86] [EL = 3]

3.10 Discontinuation

In an international review of discontinuation rates after 1 year of use of hormonal contraception, rates varied from 19% (for Norplant) to 62% (the combined pill).[87] Many of these data come from clinical trials in which continuation rates are almost always higher than in 'real life'. Data

specific to the UK are lacking. Discontinuation rates are higher for methods which do not require removal by a healthcare professional, as is clear from Table 3.3 (note that this table does not include any data on Implanon),[85] which shows the percentage of couples in the USA still using each method at the end of 1 year. Reasons for discontinuation are often associated with perceived risks and with real or perceived side effects. In a US study of 1657 women initiating or changing to use a new contraceptive pill, 32% of new starts and 16% of switchers had discontinued the method within six months. Of those who discontinued, 46% did so because of side effects (most of which they did not discuss with a healthcare professional and most of which would have resolved themselves within weeks).[27] In Sweden a common reason for discontinuation of the oral contraceptive pill is weight gain (perceived to be caused by the pill) and fear of health risks such as breast cancer.[29]

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

Continuation rates influence the effectiveness of contraception, since women often change to a less effective method or spend some weeks or months using no method while they decide what to use next. More than four-fifths of women in the US study who stopped the pill, despite being at risk of pregnancy, either failed to adopt another method or changed to a less effective one.[88]

Data from the US National Survey of Family Growth demonstrate high rates of method switching (61% of unmarried women will change their method over a period of 2 years).[89] Switching to a less effective method is common.[90] However, data specific to the UK are lacking.

Continuation rates of LARC are also fundamental to cost effectiveness. A method which costs £100 works out at £1.66/month if used for 5 years; discontinued after only 1 year of use the cost is £8.33/month.

3.11 Contraception and sexually transmitted infection

Sexual activity not only risks pregnancy but also sexually transmitted infection (STI) including HIV. Whilst methods of contraception are not designed to protect against STI, men and women who wish to protect themselves from STI should use a condom with every act of intercourse. Only the male condom has been shown to prevent some STIs including HIV. The sexual behaviour of potential users of contraception has relevance to method choice. For example, the IUD is relatively contraindicated for a woman with multiple partners.

LARC is not protective against STIs and HIV. There is some concern that use of hormonal methods of contraception may increase the risk of STIs including HIV.[91] (For more information see relevant chapters.)

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

RECOMMENDATIONS

Healthcare professionals providing contraceptive advice should promote safer sex. **D(GPP)**

Healthcare professionals providing contraceptive advice should be able to assess risk for sexually transmitted infections (STIs) and advise testing when appropriate. **D(GPP)**

Healthcare professionals should be able to provide information about local services for STI screening, investigation and treatment. **D(GPP)**

Table 3.3 Percentage of women continuing use at the end of the first year (United States); adapted with permission from Trussell[435]

Method	Women continuing use at one year(%)[a]
No method[b]	
Spermicides[b]	42
Withdrawal	43
Periodic abstinence	51
Calendar	
Ovulation method	
Sympto-thermal[d]	
Post-ovulation	
Cap[e]	
Parous women	46
Nulliparous women	57
Sponge	
Parous women	46
Nulliparous women	57
Diaphragm[e]	57
Condom[f]	
Female (Reality)	49
Male 53	
Combined pill and minipill	68
Evra patch	68
NuvaRing	68
Depo-Provera	56
Lunelle	56
IUD	
Progestasert (progesterone T)	81
ParaGard (copper T)	78
Mirena (LNG-IUS)	81
Norplant and Norplant-2	84
Female sterilisation	100
Male sterilisation	100

Emergency contraceptive pills: treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[g]
Lactational amenorrhea method: LAM is a highly effective, *temporary* method of contraception.[h]

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

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

[c] Foams, creams, gels, vaginal suppositories and vaginal film.

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

[e] With spermicidal cream or jelly.

[f] Without spermicides.

[g] The treatment schedule is one dose within 120 hours after unprotected intercourse, and a second dose 12 hours after the first dose.

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

NB. Some of the methods listed in this table are not available in the UK and some of the methods available in the UK are not available in the USA and therefore are not listed here. This table does not include any data on Implanon. ParaGard® is the TCu 380A IUD.

3.12 User autonomy and consent

The law and policy governing access to contraception is well developed in the UK, in that all women have had access to free contraception since 1974 via a number of providers.[92] [EL = 4] Not all methods are available to all women equally as a result of regional variation.

Globally, reproductive rights are not always recognised, leading to statements such as: 'Reproductive rights rest on the recognition of basic rights of couples and individuals to decide freely and responsibly the number and spacing and timing of their children and to have the information to do so, and the right to attain the highest standard of sexual and reproductive health.' (para 95, Beijing Platform for Action, 1995)[93]

Reproductive and sexual health care including family planning services and information is recognised as a key intervention for improving the health of women and children, but also as a human right. Right to access, choice and benefit of scientific progress (evidence-based information) are considered important in making an informed choice of contraceptive methods.[63]

For the process of seeking consent to be meaningful, refusal of treatment needs to be one of the patient's options. Competent adults are entitled to refuse treatment even when the treatment would clearly benefit their health. Ethical guidance for obtaining consent, points of law and model documentation are available.[94–97] [EL = 4]

3.13 Contraception for special groups

Adolescents

Young people aged 16 and 17 are generally presumed to have the ability to consent to their own medical treatment, including contraceptive treatment. Healthcare professionals can provide contraceptive advice and treatment to a young person under the age of 16 years without parental involvement if the young person is judged to understand the advice provided and its implications, and her/his physical or mental health would otherwise be likely to suffer, and so provision of advice or treatment is in their best interests.[98]

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

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

The consent of a competent young person cannot be overruled by a parent. If a person under the age of 18 years refuses to consent to treatment, it is possible in some cases for their parents to overrule their decision, though this is generally very rare. This right can only be exercised on the basis that the welfare of the young person is paramount. In this context welfare does not simply mean their physical health. The psychological effect of having the decision overruled would have to be taken into account and this option would normally only be pursued when the young person was thought likely to suffer 'grave and irreversible mental or physical harm' as a result of their refusal to consent to treatment.[99]

Young people under the age of 16 years have as great a right to confidentiality as any other patient. If someone under 16 is not judged mature enough to consent to treatment, the consultation itself can still remain confidential unless there are exceptional circumstances which suggest that the young person's health, safety or welfare is at risk. In this case local child protection procedures should be followed.[100] (www.dh.gov.uk/assetRoot/04/06/72/04/04067204.pdf)

The FFPRHC provides guidance on contraceptive choices for young people,[101] and DH provides guidance for healthcare professionals on the provision of contraceptive services for under-16s.[102]

People with learning disabilities

People over the age of 16 years are usually regarded as competent to decide their own treatment unless demonstrated otherwise. This applies to people with learning disabilities as much as any other person. It should not be assumed that adults or children are unable to make decisions about their own treatment simply because they have a learning disability. A key factor in assessing a person's ability to give consent is whether she/he can understand and weigh up the information needed to make the decision about contraceptive treatment. If information is presented in an appropriate way (for instance using simple language or pictorial aids) many people with learning disabilities will be able to consent to their own treatment. The involvement of specialists from learning disability teams or speech or language therapists can be helpful in assessing the individual's capacity to give consent to treatment though the patient's right to confidentiality should be borne in mind before involving anyone else.[98,103]

Currently no one else can give consent on behalf of an adult who is not judged to have the capacity to make a decision on their own behalf. However, healthcare professionals may treat the person if it would be in their best interests to do so. The High Court has ruled that 'best interests' go further than the medical interests of the person to include factors such as their general wellbeing and quality of life, their relationships with people close to them, and their religious or spiritual beliefs. Although the healthcare professional is legally responsible for deciding what is in the patient's 'best interests', any decision should ideally reflect the views of the individual's family, carers or friends. Any decision must be guided by what is genuinely in the best interests of the individual and not what would make life easier for their family or carers. Where there is serious disagreement between healthcare professionals and a patient's family that cannot be resolved, an application may be made to the High Court.[104] (www.dh.gov.uk/assetRoot/04/01/91/59/04019159.pdf)

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

People with physical disabilities

There is a tendency to assume incorrectly that men and women with physical disabilities are not sexually active and have no need of contraception.

People with learning and physical disabilities have the same right to information and help with contraception as non-disabled people. Physical disabilities may influence the acceptability, safety and appropriateness of certain methods of contraception. A woman with a disability which makes dealing with monthly menstruation and sanitary protection difficult may appreciate a method which is associated with amenorrhoea. Combined hormonal contraception (CHC) may be less safe for a woman confined to a wheelchair, since immobilisation is associated with an increased risk of venous thromboembolism and so is CHC. Insertion of an IUD, and the need to check the threads regularly, may prove difficult for some women with a disability. These factors need to be taken into consideration when discussing contraception with women with disabilities.

RECOMMENDATIONS

Healthcare professionals should be aware of the law relating to the provision of advice and contraception for young people and for people with learning disabilities. Child protection issues and the Fraser Guidelines should be considered when providing contraception for women younger than 16 years.* D(GPP)

Women with learning and/or physical disabilities should be supported in making their own decisions about contraception. D(GPP)

Contraception should be seen in terms of the needs of the individual rather than in terms of relieving the anxieties of carers or relatives. D(GPP)

Where a woman with a learning disability is unable to understand and take responsibility for decisions about contraception, carers and other involved parties should meet to address issues around the woman's contraceptive need and to establish a care plan. D(GPP)

3.14 Training of healthcare professionals in contraceptive care

Medical and nurse training are, for the most part, delivered separately. The gold standard basic competency-based training for doctors in the provision of basic sexual and reproductive healthcare, which includes contraception, is the Diploma of the Faculty of Family Planning and Reproductive Health Care (DFFP). The DFFP includes the provision of some of the long-acting methods of contraception and is currently held by approximately 10 000 doctors in the UK, many working in general practice. Additional competency-based training is required to obtain the qualifications for the provision of intrauterine methods (IUD and IUS) and for subdermal methods of contraception. These qualifications are also awarded by the Faculty of Family Planning and Reproductive Health Care and are known as letters of competence (LoC) in intrauterine techniques and in subdermal techniques, respectively. All Faculty qualifications are recertifiable on a five-yearly cycle. The Membership of the Faculty of Family Planning and Reproductive Health Care (MFFP) is specific to the field of sexual and reproductive health and is obtained through examination similar to other College memberships.

The structure of nurse education has changed and many of the old, validated courses are about to or have now expired. In the past, the national boards had responsibility for standards and curricula for training and though these were variable there was some standardisation and recognition within family planning and contraception. In the ensuing reorganisation, Scotland, Wales and Northern Ireland replaced their national boards but England did not. Standards are now the remit of the Nursing and Midwifery Council (NMC), but curricula and course structure is delegated to individual higher education institutes. This has meant that training in family planning and contraception has been addressed in different ways according to the set-up within individual universities. For example, it may be part of degrees in general practice, sexual health or women's health or as stand-alone modules in contraception, reproductive or women's health. In 2004 the Royal College of Nursing (RCN) published a Sexual Health Competency framework which was developed in partnership with a number of organisations. This framework is designed to act as a template which reflects the levels of competency expected from registered practitioner through to consultant practitioner levels, and should help to underpin training in the future.[105] The RCN recommends that all nurses working in general practice, family planning, contraception and genitourinary (GU) clinics should undertake a two-day Sexually Transmitted Infections Foundation course (STIF details are available at www.bashh.org), and that family planning and GU-trained nurses should regularly update their knowledge and skills to maintain their competence to practise. Training guidance is available from the RCN for nurses working in this field in the following areas: contraception and sexual health in primary care,[106] inserting intrauterine devices,[107] and inserting and/or removing subdermal implants.[108] Details of these are

* See the Department of Health's *Best Practice Guidance for Doctors and Other Health Professionals on the Provision of Advice and Treatment to Young People under 16 on Contraception, Sexual and Reproductive Health* (July 2004), available from www.dh.gov.uk.

available from www.rcn.org.uk. An RCN-accredited Sexual Health Skills distance-learning programme has recently been developed. It is aimed at nurses who want a holistic foundation in sexual health but who may not specialise in this field. The course is validated by the University of Greenwich.

A survey undertaken by the Contraceptive Education Service run by the Family Planning Association and the Health Education Authority identified that 88% of GPs had some training in family planning but two-thirds had family planning qualifications issued in the 1970s.[109] Just 12% had recent training, with practice nurses more likely to have attended update training courses. There are no training data available for healthcare professionals working in community contraceptive services. However, job descriptions for staff grade, associate specialist and consultants specify that candidates should hold either the diploma or membership of the Faculty of Family Planning and Reproductive Health Care or an equivalent qualification with evidence of recertification if appropriate.

For nurses working within community contraceptive services, a recognised family planning qualification or equivalent is required. Training for both nurses and doctors involves a theoretical component and practical placement. Doctors training in GU medicine now need to obtain the DFFP as part of their specialist registrar training but there is no requirement by the RCOG for specialist registrars to attend a DFFP theory course and the level of contraceptive knowledge amongst trainees could benefit from improvement.

Most of the practical, hands-on training takes place in community contraceptive services. The issues of adequate funding to support training need to be discussed locally, regionally and nationally so that the future workforce is adequately equipped to provide level one services in primary care and accurate contraceptive advice in secondary care.

RECOMMENDATIONS

Healthcare professionals advising women about contraceptive choices should be competent to: **D(GPP)**

- help women to consider and compare the risks and benefits of all methods relevant to their individual needs
- manage common side effects and problems.

Contraceptive service providers who do not provide LARC within their own practice or service should have an agreed mechanism in place for referring women for LARC. **D(GPP)**

Healthcare professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods. **D(GPP)**

3.15 Cost effectiveness of LARC methods versus other reversible contraceptive methods

The economic analysis undertaken for this guideline demonstrated that all LARC methods avert a higher number of pregnancies compared with COC and male condom, for all time frames considered in the economic model, i.e. up to 15 years of contraceptive use. For 1 year of use, two of the LARC methods, the IUD and the injectable, dominate both COC and male condom. For periods of contraceptive use equal to 2 years and above, all LARC methods dominate COC and male condom (i.e. they are not only more effective but also less costly than COC and male condom). Results of the economic analysis are reported in Chapter 8.

3.16 Brief overview of features common to progestogen-only methods

This guideline discusses four methods of LARC, the copper IUD and the three progestogen-only contraceptive methods. Common features of POC regardless of dose and route of administration are described here.

Contraception can be divided into two broad categories, hormonal and nonhormonal. There are two categories of hormonal contraception, combined (oestrogen plus progestogen) and progestogen-only. Included in the category of LARC are the copper intrauterine device and three progestogen-only methods of contraception (injectables, implants and the intrauterine system).

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

Mode of action

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

Side effects

Bleeding disturbances

Progestogen-only methods disrupt regular menstrual cycles and the resulting 'bleeding disturbance' is the most common cause for discontinuation of the method. The mechanism of action of the method determines the predominant bleeding pattern. Bleeding patterns depend on the degree of suppression of ovarian activity. If normal ovulation occurs consistently a woman will experience menstrual bleeds at a frequency characteristic of her normal cycle. If both ovulation and follicle development are completely suppressed, amenorrhoea will result and many women do experience amenorrhoea while using Depo-Provera. If ovulation or follicular development sufficient to stimulate endometrial growth occur irregularly, bleeding will be erratic and unpredictable (implants) unless there is endometrial atrophy (LNG-IUS) when, regardless of the effect on ovarian activity, amenorrhoea is common. A local effect on the endometrium of the continuous administration of progestogens also probably contributes to the bleeding patterns.

Ovarian cysts

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

Metabolic side effects of progestogens

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

Ectopic pregnancy

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

Cancer

In the large meta-analysis reporting a relative risk of 1.24 for use of the COC,[110] an increased relative risk of breast cancer for both oral and injectable progestogen-only methods of contraception (RR 1.17 for both) was demonstrated, although for injectables this was not statistically significant. In a review of other pooled analyses[111] no significant associations were found. There

are much fewer data for POC than for COC and women with risk factors for breast cancer may be preferentially prescribed POC. Recent anxieties about the contribution of progestogens to the increased risk of breast cancer associated with HRT have not yet spread to POC. There is no evidence for any increased risk of other cancers and indeed some evidence to suggest a reduction in the risk of endometrial cancer.

Cardiovascular disease including venous thromboembolism

There is no evidence for an increase in the risk of stroke, myocardial infarction or VTE in association with POC.[112] An association between VTE and progestogen used for the treatment of gynaecological conditions such as anovulatory dysfunctional uterine bleeding[113] is likely to be due to prescriber bias since the COC – often the method of choice – is contraindicated in women with known risk factors for VTE. A very weak association between use of Norplant and hypertension[114] may be due to observer bias.

A systematic review of three cohort studies and one cross-sectional study reported no significant association of high blood pressure with the use of progestogen-only pills for up to 2–3 years of follow-up.[115] [EL = 3]

Gall bladder disease

A weak association between use of Norplant and gall bladder disease[114] has been described but there is no evidence of any association with other POC.

Bone mineral density

No study has demonstrated any adverse effect of progestogen-only implants on bone mineral density. It is unlikely therefore that use of oral or intrauterine POC would be harmful. Injectable methods, however, deliver higher doses of progestogen suppressing ovarian activity and causing hypoestrogenism and loss of bone mineral density and there are concerns that their use may increase the risk of osteoporosis.[116] (Refer to the forthcoming NICE clinical guideline *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk* – www.nice.org.uk/page.aspx?o=33923.)

Return to fertility

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

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

4. Copper intrauterine devices (IUDs)

4.1 Introduction

What they are

Intrauterine devices (IUDs) are small contraceptive devices inserted through the cervix and positioned in the cavity of the uterus. Copper-containing IUDs currently available in the UK include: U-shaped (Multiload Cu375, MultiSafe 375, Multi-Safe 375 Short Loop, Load 375); plain T-shaped (Nova-T 380, Neo-Safe T 380, UT 380, UT 380 Short, Flexi-T 300); banded T-shaped (T-Safe CU 380A, Flexi-T 380, TT 380 Slimline); and frameless (GyneFix). The TT 380 Slimline is licensed for 10 years of use, the T-Safe CU 380A for 8 years and the remaining available IUDs for 5 years of use. For the purposes of the guideline we have regarded T-Safe CU 380A as comparable to TCu 380A. The available IUDs have copper on a plastic frame or a thread (frameless), with a small thread that protrudes through the cervical canal into the upper part of the vagina allowing easy removal. The tails also can be checked regularly by the wearer to ensure correct placement. It may occasionally require local anaesthesia and dilation of the cervical canal to aid insertion in nulliparous or perimenopausal women. IUDs vary in structural design and amount of copper. The levonorgestrel-only intrauterine system (LNG-IUS) has some similar features to IUDs and is considered in a separate chapter (see Chapter 5).

Mechanism of action

IUDs prevent pregnancy by impairing gamete viability at fertilisation and they have a strong inhibitory effect on implantation.[117,118] Copper ions provide most if not all of the effects.[117–121] [EL = 3]

RECOMMENDATION

Women should be informed that intrauterine devices (IUDs) act by preventing fertilisation and inhibiting implantation. **C**

Use in Great Britain

In 2003/04, it was estimated that 4% of women aged 16–49 years in Great Britain use the IUD as their method of contraception.[1] [EL = 3]

Duration of action

The IUDs currently available in the UK are licensed for a variety of time periods from 5–10 years. Studies have shown that most of the widely used copper IUDs are effective for at least 5 years and many are effective for longer.[122,123]

RCT data suggest that the TCu 380A appears effective for up to 12 years. A study combined data from two RCTs across 24 centres with a total of 3277 women and compared the effectiveness of TCu 380A and the CuT220 at 8, 10 and 12 years of use. Pregnancy rates per 100 women were significantly lower for the TCu 380A at all time points (2.2% at 8, 10 and 12 years). No pregnancies were reported among women using the TCu 380A after 8 years of use.[124] The Gyne T380 is no longer available in the UK but women with this device may continue to use it for its 10 year licensed duration.

Multiload versions containing lower amounts of copper (no longer available) were licensed for 3 years.[122] Results from three randomised trials suggest that the Multiload Cu375 is effective for 5 years (see Section 4.2).

The GyneFix is licensed for 5 years.[122] We found no evidence supporting a longer duration of use. Previous UK practice recommended that a copper IUD inserted at age 40 years or over may be retained beyond the licensed duration until contraception is no longer required.[122,123,125]

SUMMARY OF EVIDENCE

- Women using the TCu 380A for up to 12 years had low pregnancy rates (around 2%).

RECOMMENDATION

The licensed duration of use for IUDs containing 380 mm^2 copper ranges from 5 to 10 years, depending on the type of device. **D**

Women who are aged 40 years or older at the time of IUD insertion may retain the device until they no longer require contraception, even if this is beyond the duration of the UK Marketing Authorisation.* **D**

The evidence

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

In addition to reviewing evidence identified from our search strategy, we assessed studies reviewed in a Health Technology Report[126] and included those studies deemed to be appropriate to the population of the UK and developed countries in terms of body weight and access to contraceptive service provision (see Section 3.4).

4.2 Effectiveness

Framed IUDs

One RCT undertaken in Nigeria (n = 200) reported no difference in cumulative pregnancy rates among women using Multiload Cu375 (n = 100) compared with women using TCu 380A (n = 100) (0.0% versus 1.1% at 1 year).[127] [EL = 1+]

A multicentre RCT reported no difference in cumulative pregnancy rates among women using Multiload Cu375 (n = 740) compared with women using TCu 380A (n = 737) (adjusted rates 0.8% versus 0.3% at 1 year; 1.3% versus 0.6% at 2 years; 1.8% versus 0.6% at 3 years).[128,129] [EL = 1+]

Another RCT reported a significantly higher cumulative pregnancy rate in women using Multiload Cu375 (n = 948) than in women using TCu 380A (n = 946) (adjusted rates 1.4% versus 0.4% at 1 year; 2.7% versus 1.2% at 2 years).[130] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported a significantly higher cumulative pregnancy rate among women using Multiload 375 than among women using TCu 380A at 3 years (2.9% versus 1.6%) and at 10 years (5.3% versus 3.4%). The total number of women completing 10 years was 727.[131–133] [EL = 1+]

One RCT (an abstract) compared Nova-T 380 (n = 470) and Gyne T380 Slimline (n = 487) and reported significant contraceptive effectiveness in favour of Gyne T380 (rates not stated). After 12 months, there was no difference in efficacy between the two devices (rates not stated). The cumulative pregnancy rates were 3.6 per 100 woman-years among Nova-T 380 users versus 1.7

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

per 100 woman-years among Gyne T380 users at 3 years. Fifty-two percent of Nova-T 380 and 47% of Gyne T 380 completed the 3 years follow-up.[134] [EL = 1–]

A non-comparative study (n = 574) in the UK reported cumulative pregnancy rates of 0.8%, 1.6%, 2.0%, 2.0% and 2.0% among Nova-T 380 users at 1, 2, 3, 4 and 5 years, respectively.[135] [EL = 3]

Another non-comparative study (n = 400) in Finland reported cumulative pregnancy rates of 0.5 and 1.6 per 100 woman-years among Nova-T 380 users at 1 and 2 years, respectively.[136] [EL = 3]

Frameless versus framed IUDs

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

A systematic review of four RCTs[137–140] reported no significant difference in cumulative pregnancy rates between the frameless device (Cu-Fix, FlexiGard and GyneFix) and TCu 380A IUDs at 1 year (RR 1.79; 95% CI 0.81 to 3.95) and 3 years (range of 0.0% to 2.2% versus 0.3% to 1.6%) (RR 1.34; 95% CI 0.85 to 2.10).[141] [EL = 1++] In two of the trials included,[138,139] pregnancy and expulsion rates with the frameless device were higher in the first year when compared with the TCu 380A. The author suggested that this may be due to the use of a deficient introducer for the frameless IUDs in the studies.

SUMMARY OF EVIDENCE

Table 4.1 Copper IUDs: cumulative pregnancy rates

Study	Cumulative pregnancy rate (%)				Measurement point (year)	EL
	TCu 380A (licensed 8 years)	Multiload Cu375 (licensed 5 years)	Frameless (Cu-Fix, GyneFix, FlexiGard) (licensed 5 years)	Nova-T 380 (licensed 5 years)		
127	1.1	0.0			1	1+
128,129	0.3 0.6 0.6	0.8 1.3 1.8			1 2 3	1+
130	0.4 1.2	1.4 2.7			1 2	1+
131–133	1.6 3.4	2.9 5.3			3 10	1+
141	0.3–1.6		0.0–2.2		3–6	1++
135				0.8 2.0 2.0	1 3 5	3
136				0.5[a] 1.6[a]	1 2	3

[a] Rate per 100 woman-years.

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

RECOMMENDATIONS

Healthcare professionals should be aware that the most effective IUDs contain at least 380 mm² of copper and have banded copper on the arms. This, together with the licensed duration of use, should be considered when deciding which IUD to use. **B**

Women should be informed that the pregnancy rate associated with the use of IUDs containing 380 mm² copper is very low (fewer than 20 in 1000 over 5 years). **C**

Copper IUDs versus other contraceptive methods

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported cumulative pregnancy rates of 1.1 and 1.4 per 100 women-years among LNG-IUS and TCu 380A users, respectively, at 7 years.[142] [EL = 1+] Results of this RCT were documented in four other reports during the 7 year study period.[143–147]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported a significantly higher cumulative pregnancy rate among users of TCu 380A IUD when compared with LNG-IUS users at 6 years (2.0% versus 0.5%).[132,133] [EL = 1+]

One RCT compared LNG-IUS (n = 141) and Nova-T 200 IUD (n = 136) in Finland and Brazil and reported a cumulative pregnancy rate of 0.08 per 458 women-years and 0.6 per 431 women-years, respectively, at 5 years.[148] [EL = 1+] Results of this RCT were documented in three other reports during the 5 year study period.[149–151]

One European multicentre RCT compared LNG-IUS (n = 1821) and Nova-T 200 IUD (n = 937). It reported a significant difference in cumulative pregnancy rate of 0.3% versus 3.7% and 0.5% versus 5.9% in users of IUS and Nova-T 200 IUD, respectively, at 3 and 5 years, respectively.[152,153] [EL = 1+] Results of this RCT were documented in two other reports during the 5 year study period.[154,155]

A cohort study in East Africa compared women using TCu 380A (n = 343) with women using COC (n = 333) and women using DMPA (n = 400). There was no significant difference in cumulative pregnancy rates (1.5 versus 2.1 versus 0.3 per 100 women-years at 1 year).[156] [EL = 2–]

SUMMARY OF EVIDENCE

Table 4.2 Copper IUDs versus LNG-IUS: cumulative pregnancy rates

Study	Cumulative pregnancy rate (%)			Measurement point (year)	EL
	TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
154,155		3.7 5.9	0.3 0.5	3 5	1+
149–151		< 0.5[a]	< 0.5[a]	5	1+
132,133	2.0	0.5	6–7	1+	
143–145	1.4[a]		1.1[a]	7	1+

[a] Rate per 100 woman-years.

- Although there is some evidence to suggest that the IUS may be more effective than a copper IUD containing 380 mm² copper, the difference is very small and of doubtful clinical significance.
- There was insufficient evidence to make a recommendation for the comparison of effectiveness between currently available copper IUDs and other contraceptive methods.

4.3 Expulsion

Expulsion of an IUD occurs in approximately 1 in 20 women, and is most common in the first three months after insertion. Expulsion commonly occurs during menstruation.[119] [EL = 4]

Copper IUDs

RCTs comparing the TCu 380A to Multiload Cu375 reported cumulative expulsion rates ranging from 3.3% to 6.0% at 1 year, 4.5% to 6.7% at 2 years, 5.4% at 3 years and 11.2% at 10 years among TCu 380A users versus 0.0% to 4.0% at 1 year, 5.0% at 2 years, 6.5% at 3 years and 14.8% at 10 years among Multiload Cu375 users[127–133] [EL = 1+]

One RCT (an abstract) compared Nova-T 380 (n = 470) and Gyne T380 Slimline (n = 487) and reported more partial expulsions with Gyne T380 users (rates not stated).[134] [EL = 1–]

A systematic review of four RCTs [137–140] reported a significantly higher cumulative expulsion rate with the frameless IUD when compared with TCu 380A at 1 year (RR 2.48; 95% CI 1.89 to 3.26). It was suggested that this could be due to the use of a deficient introducer for the frameless IUD. Retention of the frameless device also appeared to depend on the skill and dexterity of the clinician during insertions, irrespective of the kind of introducer used. The cumulative net expulsion rates for the two groups were similar from 2 to 6 years (3.1% with FlexiGard versus 2.6% with TCu 380A) (RR 1.20; 95% CI 0.79 to 1.84). Nulliparous women were excluded in three of the studies reviewed.[141] [EL = 1++]

A non-comparative study (n = 574) in the UK reported cumulative discontinuation rates due to expulsion of 6.0%, 8.6%, 10.3%, 12.3% and 13.0% among Nova-T 380 users at 1, 2, 3, 4 and 5 years, respectively.[135] [EL = 3]

Another non-comparative study (n = 400) in Finland reported that cumulative discontinuation due to expulsion was 1.6% and 2.8% among Nova-T 380 users at 1 and 2 years, respectively.[136] [EL = 3]

SUMMARY OF EVIDENCE

- The expulsion rates are lower with TCu 380A than Multiload Cu375 at 3 years (5.4% versus 6.5%) and at 10 years (11.2% versus 14.8%).
- The expulsion rates between TCu 380A (2.6%) and frameless IUDs (3.1%) are similar between 2 and 6 years.

Table 4.3 Copper IUDs: cumulative expulsion rates

Study	Cumulative expulsion rate (%)				Measurement point (year)	EL
	TCu 380A (licensed 8 years)	Multiload Cu375 (licensed 5 years)	Frameless (Cu-Fix, GyneFix, FlexiGard) (licensed 5 years)	Nova-T 380 (licensed 5 years)		
127–131	3.3–6.0 4.5–6.7 5.4	0.0–4.0 5.0 6.5			1 2 3	1+
132,133	11.2	14.8			10	1+
141	2.6		3.1		3–6	1++
135				6.0 10.3 13.0	1 3 5	3
136				1.6 2.8	1 2	3

Copper IUDs versus LNG-IUS

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported no significant differences between LNG-IUS users and TCu 380A users in cumulative discontinuation rates due to expulsion (6.0% versus 5.5%, 7.3% versus 6.1%, 11.8% versus 7.4% and 11.8% versus 8.4% at 1, 2 , 5 and 7 years, respectively).[142–146] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported no significant difference between LNG-IUS users and TCu 380A IUD users in cumulative discontinuation rates due to expulsion (7.5% versus 8.2%) after 6 years.[132,133] [EL = 1+]

An RCT compared LNG-IUS (n = 141) and Nova-T 200 IUD (n = 136) in Finland and Brazil. It reported cumulative discontinuation rates due to expulsion of 0.6% versus 4.5%, 0.6% versus 6.1% and 2.0% versus 6.0% at 1, 2 and 5 years, respectively).[148–151] [EL = 1+]

One European multicentre RCT which compared LNG-IUS (n = 1821) and Nova-T 200 IUD (n = 937) reported cumulative rates for removal due to expulsion of 3.4% versus 3.4%, 4.2% versus 4.1%, 4.8% versus 4.8%, 4.9% versus 5.3% and 4.9% versus 5.5% at 1, 2, 3, 4 and 5 years, respectively.[152–155] [EL = 1+]

SUMMARY OF EVIDENCE

Table 4.4 Copper IUDs versus LNG-IUS: cumulative expulsion rates

Study	Cumulative expulsion rate (%)			Measurement point (year)	EL
	TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
154,155		3.4	3.4	1	1+
		4.8	4.8	3	
		5.5	4.9	5	
149–151		6.0	2.0	5	1+
132,133	8.2		7.5	6–7	1+
143–145	5.5		6.0	1	1+
	6.1		7.3	2	
	7.4		11.8	5	
	8.4		11.8	7	

- The cumulative expulsion rates between LNG-IUS and TCu 380A varied, from 7.5% versus 8.2% after 6 years to 11.8% versus 8.4% at 7 years.

RECOMMENDATIONS

Women should be informed that IUDs may be expelled but that this occurs in fewer than 1 in 20 women in 5 years. **C**

Women should be advised how to check for the presence of IUD threads and encouraged to do this regularly with the aim of recognising expulsion. **D(GPP)**

4.4 Discontinuation and reasons for discontinuation

Framed IUDs

Altered bleeding and altered bleeding with pain are the most common reasons cited for requesting IUD (Nova-T 200 and Nova-T 380) removal.[119,135] One RCT comparing the TCu 380A (n = 946) to Multiload Cu375 (n = 948) reported similar values for overall cumulative discontinuation rates (9.5% versus 8.4% and 14.5% versus 15% at 1 and 2 years, respectively). In this study, the cumulative discontinuation rates due to bleeding and pain were 14% versus 10% and 19% versus 14% at 1 and 2 years, respectively.[130] [EL = 1+]

Another RCT comparing the TCu 380A (n = 441) with Multiload Cu375 (n = 444) reported similar values for overall cumulative discontinuation rates (10% versus 12%, 20% versus 23% and 33% versus 39% at 1, 2 and 3 years, respectively). In this RCT, the discontinuation rates due to bleeding and pain were 5% versus 4%, 8% versus 8% and 9% versus 11% at 1, 2 and 3 years, respectively.[128] [EL = 1+]

One RCT undertaken in Nigeria reported overall cumulative discontinuation rates of 14.2% and 13.0% among users of TCu 380A (n = 100) and Multiload Cu375 (n = 100), respectively, at 1 year. In this RCT, the cumulative discontinuation due to PID was reported to be 1.2% versus 1.0% at 1 year.[127] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported similar overall discontinuation rates between users of TCu 380A to Multiload Cu375, at 12% versus 11%, 22% versus 22% and 60% versus 63% at 1, 3 and 10 years, respectively). Discontinuation due to PID was 0.4% versus 0.5% at 10 years.[131–133] [EL = 1+]

Frameless IUDs

A systematic review of four RCTs reported no significant differences in cumulative discontinuation rates, mainly due to expulsion, between frameless IUDs and TCu 380A at 1 year (16% versus 13%) (RR 0.97; 95% CI 0.94 to 0.99), at 3 years (28% versus 27%) (RR 0.98; 95% CI 0.95 to 1.02) and at 6 years (42% versus 40%) (RR 0.97; 95% CI 0.92 to 1.02) (results from one RCT[139]). The cumulative discontinuation rate at 3 years was 9% versus 15% in another RCT[140] (RR 1.06; 95% CI 1.00 to 1.13). There was no significant difference in removal rates due to excessive bleeding and/or pain among parous women who used either the frameless copper IUDs or the TCu 380A at 3 years (7.0% versus 8.0%) (RR 0.92; 95% CI 0.74 to 1.14). No differences were identified in cumulative rates of removal for pain alone between the two groups at 3 years (1% versus 2%) (RR 0.6; 95% CI 0.34 to 1.05). There was no significant difference in cumulative removal rates due to PID (0.1% with frameless versus 0.4% with TCu 380A at 3 years) (RR 0.80; 95% CI 0.23 to 2.81). Only one perforation with GyneFix was reported in the four RCTs reviewed.[141] [EL = 1++]

A non-comparative study (n = 574) in the UK reported cumulative discontinuation rates for all reasons of 26.2%, 40.7%, 53.0%, 62.5% and 67.5% among Nova-T 380 users at 1, 2, 3, 4 and 5 years, respectively; the corresponding cumulative discontinuation rates due to bleeding problems were 10.3%, 16.2%, 21.1%, 26.5% and 29.6%; due to pain they were 1.9%, 3.4%, 4.5%, 5.5% and 7.1%; and due to PID the rate was 0.9% throughout the 5 years.[135] [EL = 3]

Another non-comparative study (n = 400) in Finland reported cumulative discontinuation rates of 11.0% and 24.5% among Nova-T 380 users at 1 and 2 years, respectively; the corresponding cumulative discontinuation rates due to bleeding problems were 4.7% and 8.7%; and due to pain they were 1.3% and 2.3%.[136] [EL = 3]

SUMMARY OF EVIDENCE

Table 4.5 Copper IUDs: cumulative discontinuation rates

Reason for removal	Study	Cumulative discontinuation rate (%)				Measurement point (year)	EL
		TCu 380A (licensed 8 years)	Multiload Cu375 (licensed 5 years)	Frameless (Cu-Fix, GyneFix, FlexiGard) (licensed 5 years)	Nova-T 380 (licensed 5 years)		
Overall	130	9.5 14.5	8.4 15.0			1 2	1+
	128	10 20 33	12 23 39			1 2 3	1+
	131–133	12 22 60	11 22 63			1 3 10	1+

Table 4.5 Copper IUDs: cumulative discontinuation rates (continued)

Reason for removal	Study	Cumulative discontinuation rate (%)				Measurement point (year)	EL
		TCu 380A (licensed 8 years)	Multiload Cu375 (licensed 5 years)	Frameless (Cu-Fix, GyneFix, FlexiGard) (licensed 5 years)	Nova-T 380 (licensed 5 years)		
	141	15–27		10–29		3	1++
	135				26.2 53.0 67.5	1 3 5	3
	136				11 25	1 2	3
Bleeding and pain	128	5 8 9	4 8 11			1 2 3	1–
	130	14 19	10 14			1 2	1+
	128	5 8 9	4 8 11			1 2 3	1+
	141	8.0		7.0		3–6	1++
Bleeding only	135				10.3 21.1 29.6	1 3 5	3
	136				4.7 8.7	1 2	3
PID	132,133	0.4	0.5			10	1+
	127	1.2	1.0			1	1+
	130	1.3	0.6			2	1+
	128,129	7.0	4.6			3	1+
	141	0.4		0.1		3–6	1++
	135				0.9	5	3

- The cumulative discontinuation rate for all reasons is similar between different copper IUDs. Over 5 years of use, between 1 in 4 and 1 in 2 women will stop using the method.
- The cumulative discontinuation rate for all reasons is similar between frameless IUDs and the TCu 380A (below 30% at 3 years). The cumulative discontinuation rate is also similar due to bleeding and pain (around 8% at 3 years).
- The most common side effect that leads to discontinuation of copper IUDs is bleeding problems.

Copper IUDs versus LNG-IUS

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a significant difference in cumulative discontinuation rates between LNG-IUS users and TCu 380A users (24% versus 18%, 40% versus 31%, 51% versus 41%, 59% versus 52%, 67% versus 60% and 77% versus 72% at 1, 2, 3, 4, 5 and 7 years, respectively). There were significant differences in cumulative discontinuation rates due to amenorrhoea (4.9% versus 0.1%, 8.4% versus 0.2%, 19.7% versus 0.4% and 24.6% versus 1.1% at 1, 2, 5 and 7 years, respectively). The annual discontinuation rates due to amenorrhoea ranged from 2.5% to 6.6 % in the first 5 years. The

cumulative discontinuation rates due to other menstrual problems and pain were not significantly different at 1 and 2 years (6.0% versus 7.0% and 8.6% versus 11.3%, respectively) but were significantly different at 5 and 7 years (15.4% versus 23.0% and 20.4% versus 30.0%, respectively). There were no significant differences between the two groups in cumulative discontinuation rates due to PID (0.9% versus 0.8%, 1.4% versus 1.2% and 1.6% versus 1.5% at 1–2, 3–5 and 6–7 years, respectively).[142–146] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported a significant difference in discontinuation rates due to bleeding problems between LNG-IUS users (n = 464) and TCu 380A IUD users (n = 580) at 6 years (36.0% versus 11.0%). There were significant differences in discontinuation rates due to amenorrhoea (23.5% versus 0.5%), reduced bleeding (10.9% versus 3.1%) and increased bleeding (5.4% versus 7.2%) in the two groups at 6 years. There was no significant difference in discontinuation rates due to PID (0.3% versus 0.1%) at 6 years.[132] [EL = 1+]

An RCT which compared IUS (n = 141) and Nova-T 200 IUD (n = 136) in Finland and Brazil reported cumulative discontinuation rates of 16% versus 14%, 33% versus 28% and 45% versus 50% at 1, 2 and 5 years, respectively. There was a significant difference in the cumulative discontinuation rates due to amenorrhoea in the two groups (2.6% versus 0.0%, 10.7% versus 0.0% and 13.0% versus 0.0% at 1, 2 and 5 years, respectively). The data for the cumulative discontinuation rates due to other menstrual problems and pain were 6.5% versus 3.5%, 7.5% versus 7.1% and 8.3% versus 21.7% at 1, 2 and 5 years, respectively.[148–151] [EL = 1+]

One European multicentre RCT which compared IUS (n = 1821) with Nova-T 200 IUD (n = 937) reported cumulative discontinuation rates of 20% versus 17%, 34% versus 29%, 43% versus 41%, 49% versus 49% and 53% versus 56% at 1, 2, 3, 4 and 5 years, respectively. The cumulative rate for removal due to amenorrhoea was significantly higher in users of IUS than Nova-T 200 (1.5% versus 0.0%, 2.9% versus 0.0%, 3.6% versus 0.0%, 4.2% versus 0.0% and 4.3% versus 0.0% at 1, 2, 3, 4 and 5 years, respectively). The cumulative rate for removal for other bleeding problems and pain were 7.4% versus 7.3%, 11.1% versus 11.6%, 13.0% versus 15.3%, 14.2% versus 18.1% and 15.1% versus 20.4% at 1, 2, 3, 4 and 5 years, respectively. The corresponding cumulative rates for removal due to PID were 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5%, and 0.6% versus 1.6%. Significant differences were also reported in removal rates between IUS and IUD due to depression (2.9% versus 0.0%), acne (2.3% versus 0.4%), headache (1.9% versus 0.25%) and weight change (1.5% versus 0.0%) at 5 years.[152–155] [EL = 1+]

SUMMARY OF EVIDENCE

Table 4.6 Copper IUDs versus LNG-IUS: cumulative discontinuation rates

Reason for removal	Study	Cumulative discontinuation rate (%)			Measurement point (year)	EL
		TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
Overall	154,155		17	20	1	1+
			41	43	3	
			56	53	5	
	149–151		14	16	1	1+
			28	33	2	
			50	45	5	
	143–145	18		24	1	1+
		41		51	3	
		60		67	5	
		72		77	7	
Amenorrhoea	154,155		0.0	1.5	1	1+
			0.0	3.6	3	
			0.0	4.3	5	
	149–151		0.0	2.6	1	1+
			0.0	10.7	2	
			0.0	13.0	5	

Table 4.6 Copper IUDs versus LNG-IUS: cumulative discontinuation rates (continued)

Reason for removal	Study	Cumulative discontinuation rate (%)			Measurement point (year)	EL
		TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
	149–151		0.0	2.6	1	1+
			0.0	10.7	2	
			0.0	13.0	5	
	143–145	0.1		4.9	1	1+
		0.2		8.4	2	
		0.4		19.7	5	
		1.1		24.6	7	
	132,133	0.5		23.5	6–7	1+
Bleeding and pain	154,155		7.3	7.4	1	1+
			15.3	13.0	3	
			20.4	15.1	5	
	149–151		3.5	6.5	1	1+
			7.1	7.5	2	
			21.7	8.3	5	
	143–145	7.0		6.0	1	1+
		11.3		8.6	2	
		23.0		15.4	5	
		30.0		20.4	7	
Bleeding only	132,133	11.0		36.0	6–7	1+
PID	154,155		0.4	0.3	1	1+
			1.5	0.5	3	
			1.6	0.6	5	
	143–145	0.8		0.9	1–2	1+
		1.2		1.4	3–5	
		1.5		1.6	6–7	
	132,133	0.1		0.3	6–7	1+

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

RECOMMENDATION

Healthcare professionals should be aware that:

- up to 50% of women stop using IUDs within 5 years
- the most common reasons for discontinuation are unacceptable vaginal bleeding and pain.

C

4.5 Adverse effects

Bleeding problems

(See Section 4.4 for discontinuation rates.)

It has been reported that although IUDs do not affect ovulation, the onset of menstrual bleeding occurs earlier than in normal cycles.[157]

Copper IUDs

One RCT reported no difference in the rates of menorrhagia (4% versus 5%) among users of TCu 380A (n = 100) and Multiload Cu375 (n = 100) 1 year after IUD insertion. The corresponding rates for amenorrhoea were 2% versus 2%, for intermenstrual bleeding 6% versus 4%, and for dysmenorrhoea 27% versus 24%.[127] [EL = 1+]

Another RCT reported no difference in the rates of hospitalisation for heavy menstrual bleeding (0.3% versus 0.3%) among users of TCu 380A (n = 737) and Multiload Cu375 (n = 740) at 1 year. In this study the rates for intermenstrual bleeding (not requiring hospitalisation) were 8.3% versus 9.7%, and for dysmenorrhoea 48.6% versus 44.5%.[129] [EL = 1+]

SUMMARY OF EVIDENCE

- IUD use is associated with increased bleeding problems and dysmenorrhoea but 1 year after insertion there is no significant difference in the rates of problems comparing TCu 380A, Multiload Cu375 and MLCu380.

RECOMMENDATION

Women should be informed of the likelihood of heavier bleeding and/or dysmenorrhoea with IUD use. **C**

Copper IUDs versus other contraceptive methods

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported that LNG-IUS (n = 1125) users were more likely to experience amenorrhoea than TCu 380A IUD users (n = 1121) at 3 months (RR 2.15; 95% CI 1.31 to 3.56) and at 3 years (RR 7.24; 95% CI 4.14 to 12.65). No significant differences were noticed between the two groups in terms of prolonged bleeding at 3 months and 1 year. For LNG-IUS users, amenorrhoea, spotting, menorrhagia, dysmenorrhoea and premenstrual syndrome all occurred at a significantly higher incidence in the first 2 years after insertion than at 3 and 4 years. The incidence of these bleeding disturbances declined further at 6 years and later years. Women aged 30 years or over using LNG-IUS were significantly less likely to report amenorrhoea, oligomenorrhoea and dysmenorrhoea than were younger women.[142] [EL = 1+]

Re-analyses of menstrual diaries (n = 287) from one RCT[153] investigated bleeding patterns in women with post-abortal and post-menstrual insertion of Nova-T 200 IUD and LNG-IUS. Nova-T 200 IUD users had more bleeding days than LNG-IUS users. Women receiving LNG-IUS post-abortally had fewer bleeding days than women receiving it post-menstrually. The removal of the superficial endometrium during abortion may result in these improved bleeding patterns.[158] [EL = 1+]

SUMMARY OF EVIDENCE

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

Management of bleeding problems

Heavier and longer menstrual bleeding can be treated with NSAIDs such as mefenamic acid or antifibrinolytics, including tranexamic acid.

One RCT (n = 25) reported a significant reduction in mean total blood loss during treatment with mefenamic acid when compared with placebo.[159] [EL = 1–] Another RCT (n = 19) compared tranexamic acid, diclofenac sodium and placebo in the treatment of excessive blood loss in IUD

users (types not specified). It reported significant reduction by 54% in mean blood loss in IUD users treated with tranexamic acid when compared with placebo. Treatment with diclofenac sodium also reduced blood loss by 20% when compared with placebo. Neither treatment reduced pelvic discomfort during menstruation or shortened its duration.[160] [EL = 1+] One crossover RCT (n = 20) reported significant reduction in menstrual loss in IUD users (Copper 7, copper T220, copper T380 and Lippes Loop, all unlicensed) treated with ibuprofen when compared with placebo.[161] [EL = 1–] Another crossover RCT (n = 34) reported significant reduction in menstrual bleeding in IUD (types not specified) users treated with high- and low-dose naproxen when compared with placebo.[162] [EL = 1–]

A cohort study reported that complaints of bleeding were not associated with a misplaced device demonstrated by ultrasound scan but this should be considered in women with persistent bleeding.[163] [EL = 2–] A secondary analysis of this data suggested that position is influenced by growth and thinning of endometrium.[164] [EL = 3]

WHOSPR recommends a short course of NSAIDs, taken during the days of bleeding, to treat spotting or light bleeding. Gynaecological pathology, pregnancy and infection should be excluded if abnormal bleeding persists.[77] [EL = 4]

SUMMARY OF EVIDENCE

- NSAIDs and tranexamic acid are effective in the treatment of heavy bleeding with IUD use.

RECOMMENDATIONS

Women should be informed that heavier bleeding and/or dysmenorrhoea are likely with IUD use. **C**

Healthcare professionals should be aware that heavier and/or prolonged bleeding associated with IUD use can be treated with non-steroidal anti-inflammatory drugs and tranexamic acid. **B**

Women who find heavy bleeding associated with IUD use unacceptable may consider changing to a levonorgestrel intrauterine system (LNG-IUS). **D(GPP)**

Anaemia

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

One RCT compared MBL and haematological parameters in Multiload Cu250 users (n = 16) and Multiload Cu375 users (n = 18). It reported a significant increase in MBL from baseline in both groups at 3 months. This increase remained unchanged throughout 12 months. There was no significant difference in MBL between the two groups prior to insertion, or at 3, 6 and 12 months. There was no significant difference in haematological parameters (haemoglobin, haematocrit, erythrocyte count and ferritin) between the two groups before or after IUD use. The haemoglobin concentrations were 135 g/l and 133 g/l for Multiload Cu250 users before and 3 years after the study, respectively. The corresponding data for the Multiload Cu375 were 139 g/l and 137 g/l. The women enrolled for this study were healthy and had regular menstrual cycles.[165] [EL = 1–] This RCT was continued for 3 years and no significant differences were reported between the two groups in MBL and haematological parameters.[166] [EL = 1–]

SUMMARY OF EVIDENCE

- Increased menstrual blood loss is common with use of copper IUDs.

4.6 Common concerns and symptoms

Weight change

Weight fluctuation in women of reproductive age is common, whether or not hormonal contraceptives are used. The prevalence of being overweight is increasing worldwide. It is

estimated that 25% of women in the UK are categorised as obese.[167] A 7-year case note review of copper IUD users in Brazil (n = 1679) reported a tendency to gain weight during the women's reproductive years, regardless of the contraceptive methods used. In this study, older women tended to gain more weight than younger women.[168] [EL = 3]

A European RCT reported no evidence of a difference in body weight change among women using the copper-releasing Nova-T 200 IUD (n = 937) or the hormone-releasing LNG-IUS (n = 1821). In this study, the mean weight at baseline was 61.6 (SD 10.6) kg in the Nova-T 200 group and 62.0 (SD 10.0) kg in the LNG-IUS group. The mean weight had increased to 64.4 kg in both groups at 5 years (a mean increase of 2.5 kg in the Nova-T 200 group versus 2.4 kg in the LNG-IUS group). Removal of the device due to weight gain was, however, significantly different between LNG-IUS (1.5%) and IUD users (0%).[153] [EL = 1+]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a significant difference in the occurrence of weight gain (0.7% in the LNG-IUS group versus 0.4% in the TCu 380A group), but no difference in the discontinuation rate due to weight gain or weight loss over the 7 years.[142] [EL = 1+]

A 5 year multicentre controlled cohort study (n = 16 021), undertaken mainly in developing countries, reported significant difference in frequency of reported weight gain among users of Norplant, IUD (copper and non-copper) and sterilisation (4.5 % versus 0.9 % versus 0% per 1000 woman-years, respectively). For reported weight loss, the data were 1.2 % versus 0.5% versus 0.1 % per 1000 woman-years.[114] [EL = 2–]

SUMMARY OF EVIDENCE

- There is no evidence of significant weight change between IUD and IUS users in European studies.

RECOMMENDATION

Women should be informed that there is no evidence that IUD use affects weight. C

Altered libido and mood

The experience of sexual dysfunction, such as loss of libido, is common among young women, ranging from 5–10% in one literature review[169] to about 30% in a national survey in the USA.[170]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported no difference in the occurrence of 'frigidity' (0.4% in the LNG-IUS group versus 0.4% in the TCu 380A IUD group), or depression (1.2% versus 1.1%).[142] [EL = 1+]

A cohort study (n = 1073) reported no differences in a decrease of sexual desire between OC and IUD (Multiload Cu375, Nova-T 200, Gyne T380) users (OR 1.32; 95% CI 0.70 to 2.49). However, sexual desire decreased with age and was lower in nulliparous women and in those with an average or poor relationship with their partners.[171] [EL = 2–]

A 5 year multicentre controlled cohort study (n = 16 021), undertaken mainly in developing countries, reported significantly fewer women with mood disorders whilst using IUDs (copper and non-copper) compared with Norplant and sterilisation (1.2 versus 2.8 versus 2.2 per 1000 woman-years). The figures for premenstrual tension were 0.7 versus 1.3 versus 0.8 per 1000 woman-years.[114] [EL = 2–]

SUMMARY OF EVIDENCE

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

RECOMMENDATION

Women should be informed that any changes in mood and libido are similar whether using IUDs or the IUS, and that the changes are small. C

4.7 Risks

Cardiovascular disease

A cohort study in Thailand comparing long-term DMPA users (n = 50) with TCu 380A users (n = 50) reported no significant difference in systolic and diastolic blood pressure between the two groups at 120 months.[172] [EL = 2+]

In the current WHO-MEC recommendations, copper IUDs are assigned to category '2' for women with valvular heart disease. WHO-MEC recommends that prophylactic antibiotics be used at the time of insertion to prevent endocarditis.[63] A small study identified transient bacteraemia from vaginal organisms in 13% of women within 10 minutes of IUD replacement/insertion.[173] [EL = 3]

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

Ectopic pregnancy

An ectopic pregnancy refers to any pregnancy that occurs outside the uterus. The absolute risk of ectopic pregnancy (i.e. the risk that a woman will experience an ectopic pregnancy) is a function of the absolute risk of pregnancy in combination with the conditional risk of ectopic pregnancy (i.e. the risk that a pregnancy will be ectopic). The ectopic pregnancy rate in women generally increases with age. However, all methods of contraception decrease the risk of ectopic pregnancy as they reduce the absolute risk of pregnancy. The **relative** likelihood of a pregnancy being ectopic is greatly increased when a woman becomes pregnant during use of an IUD.[174] It is estimated that 1.4 per 100 pregnancies in women using no contraception is likely to be an ectopic pregnancy versus the conditional risk of annual ectopic pregnancy of 6 per 100 pregnancies (6%) among IUD users.[117,175]

Copper IUDs

Interim results from a WHO international multicentre RCT reported significantly higher cumulative ectopic pregnancy rates among women using Multiload Cu375 than women using TCu 380A at 3 years (2.8% versus 1.4%). After 10 years, women using TCu 380A had a significantly| higher cumulative ectopic pregnancy rate than women using the Multiload Cu375. (0.8% versus 0.1%). The total number of women completing 10 years was 727.[131–133] [EL = 1+]

A systematic review of four RCTs[137–140] reported low ectopic pregnancies in users of both frameless IUDs and TCu 380A. One of the studies reviewed[139] reported no significant difference in cumulative ectopic pregnancies, with a rate of 0.06% among users of the frameless IUD compared with 0.46% with users of TCu 380A (RR 0.20; 95% CI 0.02 to 1.65).[141] [EL = 1++]

One RCT comparing TCu 380A IUDs with TCu220 IUDs (unlicensed) reported cumulative discontinuation rates due to ectopic pregnancy of 0.1% at 3 and 5 years, and 0.4% among TCu 380A users at 8 and 10 years.[124] [EL = 3]

A secondary analysis of a number of studies estimated absolute annual ectopic pregnancy rates of 0.02 per 100 TCu 380A users and 0.3 to 0.5 per 100 non-contraceptors, taking into consideration the conditional risk of annual ectopic pregnancy of 6 per 100 pregnancies (6%) among TCu 380A users and 1.4 among non-contraceptors (1.4%). This study reported ectopic pregnancy rates of 0.2 ± 0.1 per 1000 women-years for both TCu 380A and Multiload Cu375 users at 2 years.[117,175] [EL= 2+]

SUMMARY OF EVIDENCE

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

Copper IUDs versus other contraceptive methods

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a cumulative ectopic pregnancy rate of 0.6 versus 0.0 per 1000 woman-years among TCu 380A and LNG-IUS users, respectively, at 5 and 7 years.[143,144] [EL = 1+]

One European multicentre RCT compared LNG-IUS (n = 1821) and Nova-T 200 IUD (n = 937). The cumulative ectopic pregnancy rates were 0.02 versus 0.25 per 100 woman-years in the LNG-IUS group compared with the Nova-T 200 group, respectively, during the 5 year period.[153] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported no significant difference in the cumulative discontinuation rates due to ectopic pregnancy among users of TCu 380A IUD and LNG-IUS after 6 years (0.1% versus 0.0%).[132,133] [EL = 1+]

A 5 year multicentre controlled cohort study (n = 16 021), undertaken mainly in developing countries, reported cumulative ectopic pregnancy rates for users of copper IUDs (n = 18), Norplant (n = 10) and sterilisation (n = 1) of 0.68 versus 0.30 versus 0.13 per 1000 women-years.[176] [EL = 2–]

A multinational case–control study (n = 1108) reported that a past history of PID or sexually transmitted disease in current IUD users was associated with an increased risk of ectopic pregnancy compared with pregnant and non-pregnant controls. IUD use prior to conception among pregnant women did not affect the risk of ectopic pregnancy.[177] [EL = 2–]

SUMMARY OF EVIDENCE

- The ectopic pregnancy rate is higher in copper IUDs than LNG-IUS but the rate is very low and is not clinically significant.

RECOMMENDATIONS

Women should be informed that the risk of ectopic pregnancy when using IUDs is lower than when using no contraception. **D**

Women should be informed that the overall risk of ectopic pregnancy when using the IUD is very low, at about 1 in 1000 in 5 years. **C**

If a woman becomes pregnant with the IUD in situ, the risk of ectopic pregnancy is about 1 in 20, and she should seek advice to exclude ectopic pregnancy. **C**

Actinomyces-like organisms

Actinomyces israelii are commensal bacteria of the female genital tract. *Actinomyces*-like organisms (ALOs) are found in women with and without an IUD.[178–181] The role of ALOs in IUD users is unclear.[182] They may be identified on cervical smears, but have not been shown to be predictive of any disease.[121,183–185]

Copper IUDs

IUDs users may have a higher risk of infection with ALOs compared with non-users. A non-comparative study of asymptomatic IUD users with untreated ALOs followed up for 2 years reported no occurrence of PID.[186] [EL = 3]

Copper IUDs versus other contraceptive methods

A Swiss study of 156 women found the incidence of ALOs to be significantly higher among women using Multiload Cu375 than women using LNG-IUS (20% versus 2.9% at 22 months of follow-up).[187] [EL = 3] However, differences between the prevalence rates may be attributable to cervical sampling and staining techniques, population characteristics, and the potential for bias associated with retrospective reviews of case notes.

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a similarly low incidence of ALOs on cervical smears (0.0% versus 0.1%) in both the LNG-IUS and the TCu 380A IUD group.[142] [EL = 1+]

Previous recommendations suggested follow-up every 6 months for a woman choosing to continue using an IUD in the presence of ALOs.[188] [EL = 4]

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

RECOMMENDATION

The presence of *Actinomyces*-like organisms on a cervical smear in a woman with a current IUD requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. **D(GPP)**

Pelvic inflammatory disease

A major cause of PID is *Chlamydia trachomatis*, a sexually transmitted infection of the genital tract. PID results in chronic abdominal pain, ectopic pregnancy and can lead to tubal factor infertility.[189] *Chlamydia trachomatis* is the most common STI in the UK and Europe, present in 11% of the sexually active population aged 19 or younger.[190] [EL = 3] Asymptomatic chlamydial infection can only be detected by screening. Uterine instrumentation carried out as part of IUD insertion may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic PID. The Chief Medical Officer's Advisory Group on *Chlamydia trachomatis* recommends consideration of opportunistic screening of any woman undergoing instrumentation of the uterus because of a resultant risk of ascending infection.[191] [EL = 4]

The annual incidence of PID is estimated to be 1–2% in women of reproductive age in the USA.[192] A review of the WHO's IUD clinical data from 12 RCTs (n = 22 908 insertions, 51 399 woman-years of follow-up) reported an incidence of PID of 1.6 per 1000 woman-years, whichever type of IUD was used. PID was significantly associated with the insertion of the IUD within the first 20 days (RR 6.30; 95% CI 3.42 to 11.6) and with women below the age of 25 years (RR 2.45; 95% CI 1.36 to 3.85).[193] [EL = 2+]

Copper IUDs

(See section 4.4 for discontinuation rates.)

A systematic review of four RCTs reported no significant difference in cumulative removal due to PID (0.1% with frameless versus 0.4% with TCu 380A at 3 years) (RR 0.80; 95% CI 0.23 to 2.81).[141] [EL = 1++]

Discontinuation due to PID was reported to be 1.2% versus 1.0% among users of TCu 380A and Multiload Cu375, respectively, at 1 year.[127] [EL = 1+]

A multicentre RCT reported the cumulative rate of PID among TCu 380A and Multiload Cu375 users at 3 years (7.0% versus 4.6%).[128,129] [EL = 1+]

Another RCT reported no significant difference in cumulative PID rates of 1.3% versus 0.6% among TCu 380A and Multiload Cu375 users at 2 years.[130] [EL = 1+]

A non-comparative study (n = 574) in the UK reported a cumulative discontinuation rate of 0.9% due to PID at 5 years among Nova-T 380 users.[135] [EL = 3]

Copper IUDs versus other contraceptive methods

(See Section 4.4 for discontinuation rates.)

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported no significant differences between LNG-IUS users and TCu 380A users in cumulative discontinuation rates due to PID (0.9% versus 0.8%, 1.4% versus 1.2%, and 1.6% versus 1.5% at 1–2, 3–5 and 6–7 years, respectively).[142–146] [EL = 1+]

One European multicentre RCT, which compared IUS (n = 1821) and Nova-T 200 IUD (n = 937), reported cumulative rates for removal due to PID of 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5% and 0.6% versus 1.6% at 1, 2, 3, 4 and 5 years, respectively.[152–155] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) showed no significant difference in cumulative discontinuation rates due to PID between LNG-IUS users and TCu 380A IUD users at 6 years (0.3% versus 0.1%).[132,133] [EL = 1+]

A 5 year multicentre controlled cohort study (n = 16 021), undertaken mainly in developing countries, reported the occurrence of acute PID in IUD (copper and non-copper) users (n = 18) compared with Norplant (n = 6) and sterilisation (n = 2) (0.6 versus 0.2 versus 0.3 per 1000 women-years).[176] [EL = 2–]

For IUD users who have been diagnosed with PID, testing for relevant organisms and appropriate antibiotics should be initiated. The UKSPR recommends that removing the IUD provides no additional benefit once PID is being treated with appropriate antibiotics.[79] [EL = 1–4]

Prevention of PID

A meta-analysis of four RCTs reported little benefit with prophylactic antibiotic use to cover IUD insertion among women at low risk for STI. Women at low risk of STIs who use IUDs have a low risk of PID. Overall, the odds ratios for PID associated with use of prophylactic doxycycline 200 mg or azithromycin 500 mg compared with placebo or no treatment was 0.89 (95% CI 0.53 to 1.51). Use of prophylaxis was associated with a small reduction in unscheduled visits to the provider (OR 0.82; 95% CI 0.70 to 0.98). Use of doxycycline or azithromycin had little effect on the likelihood of removal of the IUD within 90 days of insertion (OR 1.05; 95% CI 0.68 to 1.63).[194] [EL = 1++] In two RCTs included in this review, users of the TCu 380A showed no significant difference in the occurrence of PID with or without prophylactic antibiotic use, with respective odds ratios of 1.0 (95% CI 0.06 to 15.95)[195] and 0.98 (95% CI 0.06 to 15.73).[196] [EL = 1–]

RECOMMENDATIONS

Women should be informed that the risk of developing pelvic inflammatory disease following IUD insertion is very low (less than 1 in 100) in women who are at low risk of sexually transmitted infections (STIs). **C**

Uterine perforation

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

Copper IUDs

One RCT undertaken in Nigeria (n = 200) reported no perforation among Multiload Cu375 users (n = 100) compared with one perforation among TCu 380A users (n = 100) at 1 year.[127] [EL = 1+]

A multicentre RCT reported no perforation among women using Multiload Cu375 (n = 740) or TCu 380A (n = 737) at 3 years.[128,129] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported no perforation among women using Multiload 375 compared with women using TCu 380A at 3 years. No data on perforation were available at 10 years.[131–133] [EL = 1+]

A systematic review of four RCTs evaluated the effectiveness of frameless IUDs and TCu 380A IUDs. It reported one perforation with GyneFix and none with TCu 380A IUDs.[141] [EL = 1++] No perforations were reported in an audit of 138 insertions of GyneFix IUDs. The authors commented on the importance of the skills and dexterity of the clinician during insertion of the frameless device which needs to be implanted with precision into the myometrium. The anchoring technology of the frameless IUD requires skills and competence to avoid complications.[197] [EL = 3]

Another non-comparative study (n = 8343) in Turkey reported a incidence of 2.2 perforation per 1000 insertions of TCu 380A IUD at 1 year. The risk of perforation may be associated with insertion 0–3 months postpartum.[198] [EL = 3]

A non-comparative study (n = 574) in the UK reported no perforations after insertion of Nova-T 380 at 5 years.[135] [EL = 3]

A non-comparative study (n = 17 469) from New Zealand reported an incidence of perforation of 1.6 per 1000 Multiload Cu375 insertions over 6 years. Of the 28 perforation events reported, 27 were related to IUD insertion and one was related to the introduction of the uterine sound prior to insertion of the device. This reported incidence is almost certainly an underestimate, as many perforations probably go unrecognised and events not requiring hospital treatment may not have been reported.[199] [EL = 3]

Another study, using an international dataset of over 21 500 insertions, estimated the perforation rate to be 1.5 per 1000 insertions among TCu 380A users and 2.3 per 1000 insertions among Multiload Cu375 users.[200] [EL = 3]

Copper IUDs versus LNG-IUS

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a similarly low discontinuation rate due to uterine perforation (0.1% versus 0.0%) and cervical perforation (0.0% versus < 0.1%) between LNG-IUS users and TCu 380A users at 7 years.[142] [EL = 1+]

The FFPRHC endorses a 6 week interval after an asymptomatic, suspected perforation before IUD insertion is attempted again.[201] [EL = 4]

SUMMARY OF EVIDENCE

- The risk of uterine perforation associated with IUD and LNG-IUS use is low: less than 0.1%.

RECOMMENDATIONS

Women should be informed that the risk of uterine perforation at the time of IUD insertion is very low (less than 1 in 1000). **D**

Women should be informed about symptoms of uterine perforation or infection that would warrant an early review of IUD use. **D(GPP)**

Contraceptive care providers should be aware that the risk of perforation is related to the skill of the healthcare professional inserting the IUD. **D(GPP)**

Women who become pregnant while using an IUD

Approximately 6% of pregnancies occurring in women using an IUD are ectopic.[117] IUDs should not be used during pregnancy and they are assigned to category '4' by WHO-MEC.[63]

Miscarriage is the most frequent complication of pregnancy with an IUD in place. About 50% to 60% of intrauterine pregnancies miscarry if the IUD is not removed, against a background rate of 13%.[202] [EL = 3]

If pregnancy occurs with an IUD *in situ*, removal of the IUD to avoid the risk of miscarriage, preterm delivery and infection is recommended by the UKSPR.[79] [EL = 4]

RECOMMENDATIONS

Women with an intrauterine pregnancy with an IUD *in situ* should be advised to have the IUD removed before 12 completed weeks' gestation, whether or not they intend to continue the pregnancy. **D(GPP)**

4.8 Return to fertility

Data for nulliparous women from a cohort study (n = 1071) suggested that long-term IUD use was associated with reduced fertility.[203] These findings may be explained by bias (IUD users differed from non-IUD users in that they were older, had higher rates of previous miscarriage, termination and ectopic pregnancy) or confounding factors (STIs may have accounted for these findings rather than the IUD itself).[204] It was suggested that reinsertion of IUDs which were licensed for use for no more than 2 or 3 years could lead to an increase in PID, leading to reduced fertility.[205] [EL = 3]

A cohort study in New Zealand assessed fertility rates and pregnancy outcomes after removal of a variety of copper intrauterine contraceptive devices in nulligravid women (n = 375) and gravid women (n = 676). Within 48 months, 91.5% of the nulligravid women and 95.7% of the gravid women had conceived. A 2 year combined study, with regard to longer use of intrauterine contraceptive devices (greater than 2 years), showed no significant reduction in fertility and no increase in ectopic pregnancy within 24 months.[206] [EL = 2+]

A case–control study found that previous copper IUD (types not specified) use in nulliparous women did not increase the risk of tubal occlusion and infertility when compared with infertile controls (OR 1.0; 95% CI 0.6 to 1.7).[207] [EL = 2–]

A multinational European RCT compared the recovery of fertility between ex-users of LNG-IUS (n = 139) and Nova-T 200 IUD (n = 71). There was no significant difference in cumulative conception rates between ex-LNG-IUS users and ex-Nova-T 200 users at 1 year (79.1% versus 71.2%) or at 2 years (86.6% versus 79.7%). Ninety-six percent of the pregnancies occurred during the first year after removal and 84% of the pregnancies in the Nova-T 200 group and 86% in the LNG-IUS group ended in live births.[155] [EL = 1+]

Another RCT reported a pregnancy rate of 96.4% in ex-LNG-IUS users (n = 60) compared with 91.1% in ex-TCu 380A IUD users (n = 50) at 1 year.[147,208] [EL = 1+]

A questionnaire survey of pregnant women in the UK reported mean time to pregnancy (TTP) of 2.0, 2.2 and 3.9 times longer after discontinuation of COC (n = 925), IUD (n = 82) and injectable (n = 62), respectively, when compared with condom use (n = 389). Conception rates within 6 months of discontinuation were 71%, 77%, 27% and 25% among users of COC, IUDs, injectable and implants (n = 4), respectively, compared with 82% among condom users. Relative to condoms, the odds of subfecundity were 1.9, 5.5 and 2.9 respectively among users of COC, injectable and short-term IUDs.[209] [EL = 3]

RECOMMENDATION

Women should be informed that there is no evidence of a delay in the return of fertility following removal or expulsion of IUDs. **C**

4.9 Details of method use

Assessment prior to insertion

(See Section 3.6.)

The WHOSPR and UKSPR recommend that physical examination, including pelvic/genital examination, medical history and STI risk assessment, are essential and mandatory before providing IUDs as a method of contraception.

Breast examination, cervical screening, routine laboratory tests, a haemoglobin test and blood pressure screening are not recommended.[77,79] [EL = 4] Women with identified risk of STI should have their decision on their chosen method of contraception reviewed and alternative methods should be discussed.

RECOMMENDATIONS

Testing for the following infections should be undertaken before IUD insertion: **D(GPP)**

- *Chlamydia trachomatis* in women at risk of STIs
- *Neisseria gonorrhoeae* in women from areas where the disease is prevalent and who are at risk of STIs
- any STIs in women who request it.

If testing for STIs is not possible, or has not been completed, prophylactic antibiotics should be given before IUD insertion in women at increased risks of STIs. **D(GPP)**

Women with identified risks associated with uterine or systemic infection should have investigations, and appropriate prophylaxis or treatment before insertion of IUDs. **D(GPP)**

Information prior to insertion

(See Section 3.5.)

RECOMMENDATIONS

Women should be informed about failure rates, benefits, risks and side effects of IUDs. **D(GPP)**

Women should be informed that insertion of an IUD may cause pain and discomfort for a few hours and light bleeding for a few days, and they should be informed about appropriate pain relief. D(GPP)

Position of IUD within the uterine cavity

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

Time of insertion of IUD

In a normal menstrual cycle

Having reasonably excluded pregnancy, an IUD may be inserted at any time during the menstrual cycle.[63] An IUD can be inserted up to 5 days after the first unprotected sexual intercourse in a cycle, or up to 5 days after the earliest date of ovulation.

When switching methods

The UKSPR and the FFPRHC both recommend that copper IUDs can be inserted immediately if it is reasonably certain that the woman is not pregnant.[79,201] [EL = 1–4]

Following abortion

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

A systematic review of nine RCTs (mostly comparing IUDs not currently used in the UK) reported that insertion of IUDs immediately after abortion is both safe and practical. IUD expulsion rates appeared higher than after interval insertions.[210] [EL = 1++] One of the RCTs from this review compared LNG-IUS with Nova-T 200 IUD inserted at the time of elective abortion. It reported significantly lower cumulative pregnancy rates (0.8% versus 9.5%) but significantly higher cumulative discontinuation rates in LNG-IUS users due to hormonal reasons (15.9% versus 3.9%) at 5 years.[211] [EL = 1+]

Case–control studies reported that the risk of uterine perforation following IUD insertion within 30 days of an abortion is low. In this study, the controls were medical and surgical controls.[212] [EL = 3] Only three perforations were identified in 2348 such insertions in a WHO study.[213] [EL = 2–] Re-admission rates for pelvic infection were not increased by IUD insertion immediately following a first-trimester abortion.[214] [EL = 3]

There are few data specifically relating to IUD insertion following medical abortion. The FFPRHC recommends that an IUD may be inserted immediately (i.e. within 48 hours) following first- or second-trimester medical abortion. Otherwise, insertion should be delayed until 4 weeks following medical abortion (as for postpartum insertions).[201] [EL = 3]

In the current WHO-MEC recommendations, copper IUDs are assigned to category '2' for insertion in women after second-trimester abortion and category '4' for insertion in women immediate after post-septic abortion.[63]

The RCOG abortion guideline recommends that IUD can be inserted immediately following a first- or second-trimester abortion.[215] [EL = 1–4]

Post delivery

A systematic review of eight RCTs (mostly comparing IUDs not currently used in the UK) reported that postpartum insertion of IUDs appeared to be safe and effective.[216] [EL = 1++] One cohort study compared insertions of the progestogen vaginal ring (n = 802) and TCu 380A (n = 734) during lactation in postpartum women (mean time of postpartum insertion 47.6 days after delivery) and reported no significant difference in pregnancy rate (1.5% versus 0.5%) and a significant difference in expulsion rate (8.1% versus 5.6%) between the two groups at 12 months.[217] [EL = 2–]

Established practice in the UK has been to delay insertion until 6–8 weeks postpartum. WHO-MEC, however, recommends that the benefits of IUD use 4 or more weeks after delivery outweigh any risks.[63] This unrestricted use includes women who are breastfeeding, not breastfeeding or who

have been delivered by caesarean section. WHO-MEC suggests an increased risk of uterine perforation if an IUD is inserted between 48 hours and 4 weeks postpartum and therefore the risks of insertion during this time generally outweigh the benefits. A review of studies provided 2 year follow-up data on 6816 woman-months of experience following IUD insertion between 4 and 8 weeks postpartum and 19 733 woman-months of experience following IUD insertion more than 8 weeks postpartum. No perforations were identified and discontinuation rates were similar in the two groups, suggesting an IUD can be inserted safely after 4 weeks postpartum.[218] [EL = 3] WHO-MEC suggests an increased risk of expulsion if an IUD is inserted within the first 48 hours postpartum, but the benefits of immediate IUD insertion generally outweigh the risks. A non-comparative study included 734 breastfeeding women with a mean time of insertion of a TCu 380A of 47.6 days postpartum (SD 9.9). It showed an expulsion rate at 12 months of 5.6 per 100 insertions.[217] [EL = 2+] Women with current puerperal sepsis should be advised against insertion of an IUD.[219] [EL = 4]

RECOMMENDATION

Healthcare professionals should be aware that, provided that it is reasonably certain that the woman is not pregnant, IUDs can be inserted:

D(GPP)

- at any time during the menstrual cycle
- immediately after first- or second-trimester abortion, or at any time thereafter
- from 4 weeks post partum, irrespective of the mode of delivery.

4.10 Training of healthcare professionals

(See Section 3.14.)

A large prospective study, which included 17 469 Multiload Cu375 insertions by 1699 doctors, reported an incidence of 1.6 uterine perforations per 1000 insertions at 6 years. Doctors who performed fewer than 10 IUD insertions in the 6 year period reported significantly more perforations than doctors who performed from 10 to 49 IUD insertions (RR 2.30; 95% CI 0.99 to 5.26) and doctors who performed from 50 to 99 IUD insertions (RR 7.30; 95% CI 0.94 to 56.30) in the same study period.[199] [EL = 3]

A secondary analysis of TCu 380A acceptors from one RCT in three developing countries compared insertion failures and complications between non-physician (n = 174) and physician insertions (n = 193). It reported an overall significantly higher cumulative discontinuation rate due to expulsion (8.6% versus 2.7%) and bleeding/pain (8.1% versus 1.4%) in the non-physician insertion group. The overall continuation rate was also lower (77.3% versus 85.5%) in this group at 12 months. This suggested that appropriate competency-based training is required by non-physicians to limit the number of expulsions and removals for bleeding and pain.[220] [EL = 2+]

A cohort study compared IUD insertions by specialist nurses (n = 22) and doctors (n = 28). It reported that adequately trained nurses were proficient and safe at IUD insertions, regardless of the woman's parity.[221] [EL = 2–]

It has been suggested that the performance of IUDs in comparative trials is often reflective of operator skills and quality of care and follow-up, rather than the nature of the device studied. [EL = 1++][141] [EL = 4][222] IUD expulsion rates were reported to be significantly higher for inexperienced inserters.[223] [EL = 1+]

The FFPRHC has specific training requirements for healthcare professionals wishing to obtain a letter of competence (LoC) in intrauterine techniques (IUT). Competence in gynaecological examination and the assessment, management and investigation of women with IUD problems are required for all healthcare professionals inserting IUDs. Recertification should ensure continuing competence. The LoC must be updated every 5 years, with at least 2 hours of relevant continuing education and a log of at least 12 insertions in 12 months or six in 6 months using at least two different types of device in unanaesthetised patients.

The Royal College of Nursing Sexual Health Forum has issued training guidance and requirements for nurses wishing to insert IUDs.[107] [EL = 4] It outlines eligibility criteria for adequate training (for example, obtain a recognised family planning/contraception qualification), and the knowledge and skills required to perform insertion and explain various aspects of care. Nurses can receive training from experienced doctors with a letter of competence in intrauterine techniques (LoC IUT). Nurses must also observe a minimum of five insertions, and fit a minimum of ten devices of varying types.

RECOMMENDATION

IUDs should only be fitted by trained personnel with continuing experience of inserting at least one IUD or one IUS a month. **C**

4.11 Specific groups

Adolescents

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

In the current WHO-MEC recommendations, copper IUDs are assigned to category '2' for women aged from menarche to under 20 years.[63]

Nulliparity

The majority of RCTs conducted have examined the use of IUDs among parous women worldwide. There is concern that nulliparity is related to an increased risk of expulsion among IUD users. In the current WHO-MEC recommendations, the copper IUDs are assigned to category '2' for nulliparous women and '1' for parous women.[63] [EL = 3]

Women over 40 years of age

An observational study followed 50 women fitted with a TCu 380A at age 40 or older and who used the device for at least 36 months.[224] [EL= 3] No pregnancies, cases of PID or expulsions occurred during the study period. Intermenstrual bleeding was the most common reported side effect (n = 15; 30%; 95% CI 17.9% to 44.6%) followed by pain and dysmenorrhoea. Similar results were reported in a smaller study of first-time IUD users over 40 years of age with 6 months of follow-up.[225] [EL = 3]

An RCT of women requesting an IUD who received either a Multiload Cu250 (n = 2856) or a Multiload Cu375 (n = 3606) analysed the safety of IUD use in different age groups.[226] [EL = 3] Pregnancy rates were lower in older women. Expulsion and bleeding and/or pain rates were higher for younger women receiving both IUD types ($p < 0.01$).

Refer to recommendation at Section 4.1.

RECOMMENDATIONS

IUDs may be used by adolescents, but STI risk should be considered where relevant. **D(GPP)**

Healthcare professionals should be aware that: **D(GPP)**

- IUD use is not contraindicated in nulliparous women of any age
- women of all ages may use IUDs.

Women with body mass index over 30 kg/m^2

We did not identify any studies which assessed the relationship between body weight and efficacy of copper IUDs. In the current WHO-MEC recommendations, copper IUDs are assigned to category '1' for women over 30 kg/m^2 body mass index.[63]

Women who are breastfeeding

A cohort study reported no increase in copper levels in breast milk in breastfeeding mothers with an IUD (TCu 380A and Cu200B) (n = 62) inserted at 10 weeks postpartum, when compared with a third group that were not using an IUD (n = 33).[227] [EL = 2–] Another cohort study reported no change in the amount and composition of breast milk between POC users (n = 42) and copper IUD users (n = 41) at 4 months follow-up.[228] [EL = 2–]

RECOMMENDATION

Healthcare professionals should be aware that IUDs can safely be used by women who are breastfeeding. **C**

4.12 Medical conditions and contraindications

Diabetes

One RCT compared the effect of IUS use (n = 29) or IUD use (n = 30) on glucose metabolism among women with uncomplicated type 1 diabetes and reported no significant differences in mean glycosylated levels, fasting-serum glucose levels and daily insulin doses between the two groups at 6 and 12 months, suggesting that both the IUD and IUS are safe contraceptive methods for women with diabetes.[229] [EL = 1+]

A literature review which evaluated contraceptive methods for women with type 1 diabetes, type 2 diabetes and those with a history of previous gestational diabetes reported no increase in PID in these women in association with copper IUDs.[230] [EL = 4]

A US non-comparative study reported that the TCu 380A is a safe and effective device for women with type 2 diabetes. Women requesting a TCu 380A (n = 176) were followed for 5 years at a family planning clinic. Participants were more likely to be obese and to have already given birth. Continuation rates were high (93% and 70%) at 1 and 3 years, respectively. The pregnancy rate was 1.57 per 100 woman-years and expulsion rate 1.96 per 100 woman-years.[231] [EL = 3] These rates are comparable with those found in randomised studies of parous women.[232] [EL = 2+]

In the current WHO-MEC recommendations, copper IUDs are assigned to category '1' for women with diabetes.[63] [EL = 4]

Epilepsy

We did not identify any studies which assessed the use of copper IUDs in women with epilepsy.

In the current WHO-MEC recommendations, copper IUDs are assigned to category '1' for women with epilepsy and who are on anti-epileptic drugs.[63] [EL = 4]

Sexually transmitted infections, HIV and AIDS

(See Section 3.11.)

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

A systematic review of three studies to update the WHO-MEC found limited data and reported no evidence of risks of pelvic infection or of transmission to partners from IUD users with HIV/AIDS. In HIV-infected and non-infected women after IUD insertion, there was no difference between the overall complications and infection-related complications at 2 years follow-up (hazard ratio 0.98; 95% CI 0.59 to 1.60; result of one cohort study). There was no significant difference in the incidence of PID, which was low in both groups (2% in HIV-infected women versus 0.4% in non-infected women). For women at risk of HIV, IUDs were associated with a non-significant decrease in seroconversion (RR 0.80; 95% CI 0.38 to 1.69; result of one study). As women at risk for HIV will also be at risk for other STIs, these women will be at increased risk of adverse outcomes such as PID if they use an IUD. There are no studies available of women at high risk of HIV.[233–236] [EL = 2–]

In the current WHO-MEC recommendations, IUDs are assigned to category '2' for initiation and continuation for women who are at high risk of HIV or who are HIV-infected. For women with AIDS, IUDs are assigned to category '3' for initiation and category '2' for continuation. For women who are clinically well on antiretroviral therapy, IUDs are assigned to category '2' for both initiation and continuation.[63]

RECOMMENDATION

Healthcare professionals should be aware that:

- IUD use is not contraindicated in women with diabetes
- emergency drugs including anti-epileptic medication should be available at the time of IUD insertion in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation
- IUD use is a safe and effective method of contraception for women who are HIV-positive or have AIDS (safer sex using condoms should be encouraged in this group).

D(GPP)

4.13 Drug interactions

Antibiotics

We did not identify any studies which assessed antibiotic drug interactions in women using copper IUDs.

In the current WHO-MEC recommendations, copper IUDs are assigned to category '1' for women who are prescribed antibiotics.[63] [EL = 1–4]

4.14 Follow-up

The UKSPR recommends a follow-up visit after the first menses, or 3–6 weeks after insertion, to exclude infection, perforation or expulsion.[79] [EL = 4] No routine regular follow-up is required.

RECOMMENDATION

A follow-up visit should be recommended after the first menses, or 3–6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be strongly encouraged to return at any time to discuss problems, if she wants to change her method of contraception, or if it is time to have the IUD removed.

D(GPP)

5. Intrauterine system (IUS)

5.1 Introduction

What it is

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

Mechanism of action

The contraceptive effects of the LNG-IUS are mediated via its progestogenic effect on the endometrium.[118] High intrauterine levels of LNG lead to functional and histological changes within the endometrium, preventing implantation.[237–239] Sperm penetration is decreased owing to changes in cervical mucus.[240] Most women (> 75%) will continue to ovulate.[241] [EL = 3]

RECOMMENDATION

Women should be informed that the intrauterine system (IUS) may act predominantly by preventing implantation and sometimes by preventing fertilisation. D(GPP)

Use in Great Britain

In 2003/04, it was estimated that 1% of women aged 16–49 years in Great Britain use LNG-IUS as their method of contraception.[1] [EL = 3]

Duration of action

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

A multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a cumulative pregnancy rate of 1.1% and 1.4% in LNG-IUS (two different dosages used, 60 mg or 46 mg levonorgestrel) and TCu 380A users, respectively, at 4 years. No pregnancies were reported among users of either device at 5, 6 and 7 years (174 LNG-IUS users and 216 TCu 380A users completing the trial).[142] [EL = 1+]

LNG-IUS users (two different dosages used, 43 mg and 56 mg levonorgestrel) from one RCT[151] were followed up in a non-comparative study in Brazil (n = 293) which reported no pregnancies in LNG-IUS users up to 7 years of use.[242] [EL = 3]

LNG-IUS (containing 46 mg levonorgestrel) users from another RCT[153] were followed up in a non-comparative European study (n = 109) reporting no pregnancies in LNG-IUS users in 7 years of continuous use. Eighty-two of these women had a new LNG-IUS inserted at 7 years. In this study LNG-IUS was reported to be safe and effective for up to 12 years, with device replacement every 5 years. At the end of the 12 year follow-up the mean age of women was 44.7 years (range 33.5 to 51.5). LNG-IUS may provide an effective method of contraception, allowing a convenient and bleeding-free transition for women in their late reproductive years.[243] [EL = 3]

RECOMMENDATIONS

Women should be informed that licensed duration of use for the IUS is 5 years for contraception. **D**

Women who are aged 45 years or older at the time of IUS insertion and who are amenorrhoeic may retain the device until they no longer require contraception, even if this is beyond the duration of UK Marketing Authorisation*. **D**

The evidence

Comparative and non-comparative studies which evaluated the effectiveness of LNG-IUS were included based on their comparability to the population of the UK and of the developed countries. Trials of effectiveness in populations of women with a lower body weight than that of the UK female population may underestimate the failure rates and side effects profile. Discontinuation rates from countries where access to contraception is limited and/or expensive may differ from those in the UK. (See Sections 3.4 and 3.10.) This criterion was also applied to one HTA report[126] (19 RCTs and 11 cohort studies) which assessed the effectiveness of LNG-IUS-20 (Mirena®) versus other forms of reversible contraceptives. We examined the studies reviewed and included those which met the selection criteria determined by the Guideline Development Group to be appropriate to the population of the UK and the developed countries in terms of body weight and access to contraceptive service provision. (See Section 3.4.)

5.2 Effectiveness

LNG-IUS versus copper IUDs

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a cumulative pregnancy rate of 1.1% and 1.4% among LNG-IUS and TCu 380A users, respectively, at 7 years.[142] [EL = 1+] Results of this RCT were documented in four other reports during the 7 year study period.[143–147]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported a significantly higher cumulative pregnancy rate among users of TCu 380A IUD when compared with LNG-IUS users at 6 years (2.0% versus 0.5%).[132,133] [EL = 1+]

One RCT compared LNG-IUS (n = 141) and Nova-T 200 IUD (n = 136) in Finland and Brazil and reported a pregnancy rate of 0.08 per 458 women-years and 0.6 per 431 women-years, respectively, at 5 years.[148] [EL = 1+] Results of this RCT were documented in three other reports during the 5 year study period.[149–151]

One European multicentre RCT compared LNG-IUS (n = 1821) and Nova-T 200 IUD (n = 937). It reported a significant difference in cumulative pregnancy rate of 0.2% versus 3.1% and 0.3% versus 4.2% in users of IUS and Nova-T 200 IUD at 3 and 5 years, respectively.[152,153] [EL = 1+] Results of this RCT were documented in two other reports during the 5 year study period.[154,155]

A non-comparative study (n = 678) from the UK reported a gross cumulative pregnancy rate of 0.6% (95% CI 0.1 to 1.6), 1.0% (95% CI 0.3 to 2.4), 1.0% (95% CI 0.3 to 2.4), 1.0% (95% CI 0.3 to 2.4) and 1.0% (95% CI 0.3 to 2.4) at 1, 2, 3, 4 and 5 years, respectively, among LNG-IUS users.[244] [EL = 3]

* 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.

SUMMARY OF EVIDENCE

Table 5.1 LNG-IUS versus copper IUDs: cumulative pregnancy rates

Study	Cumulative pregnancy rate (%)			Measurement point (year)	EL
	TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
154,155		3.7 5.9	0.3 0.5	3 5	1+ 1+
149–151		< 0.5[a]	< 0.5[a]	5	1+
132,133	2.0		0.5	6–7	1+
143–145	1.4		1.1	7	1+
244			0.6 1.0 1.0	1 3 5	3

[a] Rate per 100 woman-years.

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

RECOMMENDATION

Women should be informed that the pregnancy rate associated with the use of the IUS is very low (fewer than 10 in 1000 over 5 years). **C**

5.3 Expulsion

Expulsion of an IUD occurs in approximately 1 in 20 women, and is most common in the first three months after insertion. Expulsion commonly occurs during menstruation.[119] [EL = 4]

IUS versus copper IUDs

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported no significant differences between LNG-IUS users and TCu 380A users in cumulative discontinuation rates due to expulsion (6.0% versus 5.5%, 7.3% versus 6.1%, 11.8% versus 7.4% and 11.8% versus 8.4% at 1, 2 , 5 and 7 years, respectively).[142–146] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported no significant difference between LNG-IUS users and TCu 380A IUD users in cumulative discontinuation rates due to expulsion (7.5% versus 8.2%) after 6 years.[132,133] [EL = 1+]

An RCT compared LNG-IUS (n = 141) and Nova-T 200 IUD (n = 136) in Finland and Brazil. It reported cumulative discontinuation rates due to expulsion of 0.6% versus 4.5%, 0.6% versus 6.1% and 2.0% versus 6.0% at 1, 2 and 5 years, respectively).[148–151] [EL = 1+]

One European multicentre RCT which compared LNG-IUS (n = 1821) and Nova-T 200 IUD (n = 937) reported cumulative rates for removal due to expulsion of 3.4% versus 3.4%, 4.2% versus 4.1%, 4.8% versus 4.8%, 4.9% versus 5.3% and 4.9% versus 5.5% at 1, 2, 3, 4 and 5 years, respectively.[152–155] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rates due to expulsion of IUS of 4.5%, 5.2%, 5.5%, 5.5% and 5.9% at 1,2, 3, 4 and 5 years, respectively.[244] [EL = 3]

SUMMARY OF EVIDENCE

Table 5.2 LNG-IUS versus copper IUDs: cumulative expulsion rates

Study	Cumulative expulsion rate (%)			Measurement point (year)	EL
	TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
154,155		3.4	3.4	1	1+
		4.8	4.8	3	1+
		5.5	4.9	5	1+
149–151		6.0	2.0	5	1+
132,133	8.2		7.5	6–7	1+
143–145	5.5		6.0	1	1+
	6.1		7.3	2	
	7.4		11.8	5	
	8.4		11.8	7	
244			4.5	1	3
			5.5	3	
			5.9	5	

- The cumulative expulsion rates between LNG-IUS and TCu 380A varied, from 7.5% versus 8.2% after 6 years to 11.8% versus 8.4% at 7 years.

RECOMMENDATIONS

Women should be informed that the IUS may be expelled but this occurs in fewer than 1 in 20 women in 5 years. **C**

Women should be advised how to check for the presence of IUS threads, and encouraged to do this regularly with the aim of recognising expulsion. **D(GPP)**

5.4 Discontinuation and reasons for discontinuation

(See Section 3.10.)

LNG-IUS versus copper IUDs

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a significant difference in cumulative discontinuation rates between LNG-IUS users and TCu 380A users (24% versus 18%, 40% versus 31%, 51% versus 41%, 59% versus 52%, 67% versus 60% and 77% versus 72% at 1, 2, 3, 4, 5 and 7 years, respectively). There were significant differences in cumulative discontinuation rates due to amenorrhoea (4.9% versus 0.1%, 8.4% versus 0.2%, 19.7% versus 0.4% and 24.6% versus 1.1% at 1, 2, 5 and 7 years, respectively). The annual discontinuation rate due to amenorrhoea ranged from 2.5% to 6.6% in the first 5 years. The cumulative discontinuation rates due to other menstrual problems and pain were not significantly different at 1 and 2 years (6.0% versus 7.0% and 8.6% versus 11.3%, respectively), but were significantly different at 5 and 7 years (15.4% versus 23.0% and 20.4% versus 30.0%, respectively). There were no significant differences between the two groups in cumulative discontinuation rates due to PID (0.9% versus 0.8% ,1.4% versus 1.2%, and 1.6% versus 1.5% at 1–2, 3–5 and 6–7 years, respectively).[142–146] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) reported a significant difference in discontinuation rates due to bleeding problems between LNG-IUS users

(n = 464) and TCu 380A IUD users (n = 580) at 6 years (36% versus 11%). There were significant differences in discontinuation rates due to amenorrhoea (23.5% versus 0.5%), reduced bleeding (10.9% versus 3.1%) and increased bleeding (5.4% versus 7.2%) in the two groups at 6 years. There was no significant difference in cumulative discontinuation rates due to PID (0.3% versus 0.1%) at and after 6 years.[132,133] [EL = 1+]

An RCT which compared IUS (n = 141) and Nova-T 200 IUD (n = 136) in Finland and Brazil reported cumulative discontinuation rates of 16% versus 14%, 33% versus 28% and 45% versus 50% at 1, 2 and 5 years, respectively. There was a significant difference in the cumulative discontinuation rates due to amenorrhoea in the two groups (2.6% versus 0.0%, 10.7% versus 0.0% and 13.0% versus 0.0% at 1, 2 and 5 years, respectively). The data for the cumulative discontinuation rates due to other menstrual problems and pain were 6.5% versus 3.5%, 7.5% versus 7.1% and 8.3% versus 21.7% at 1, 2 and 5 years, respectively.[148–151] [EL = 1+]

One European multicentre RCT which compared IUS (n = 1821) and Nova-T 200 IUD (n = 937) reported cumulative discontinuation rates of 20% versus 17%, 34% versus 29%, 43% versus 41%, 49% versus 49% and 53% versus 56% at 1, 2, 3, 4 and 5 years, respectively. The cumulative rate for removal due to amenorrhoea was significantly higher in users of IUS than Nova-T 200 (1.5% versus 0.0%, 2.9% versus 0.0%, 3.6% versus 0.0%, 4.2% versus 0.0% and 4.3% versus 0.0% at 1, 2, 3, 4 and 5 years, respectively). The cumulative rates for removal for other bleeding problems and pain were 7.4% versus 7.3%, 11.1% versus 11.6%, 13.0% versus 15.3%, 14.2% versus 18.1% and 15.1% versus 20.4% at 1, 2, 3, 4 and 5 years, respectively. The cumulative rates for removal due to PID were 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5% and 0.6% versus 1.6% at 1, 2, 3, 4 and 5 years, respectively. Significant differences were also reported in removal rates between IUS and IUD due to depression (2.9% versus 0%), acne (2.3% versus 0.4%), headache (1.9% versus 0.25%) and weight change (1.5% versus 0.0%) at 5 years.[152–155] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rates of 30%, 43%, 51%, 56% and 60% at 1, 2, 3, 4 and 5 years, respectively. The corresponding figures for IUS removal due to bleeding problems (excluding amenorrhoea) were 10.5%, 12.6%, 13.7%, 14.7% and 16.7%; due to pain 2.3%, 3.5%, 3.5%, 4.3% and 4.3%; and due to PID 0.9%, 1.2%, 1.2%, 1.2% and 1.2%. There were 26 IUS removals due to oligomenorrhoea at 5 years (3.8%). The average length of use before removal of IUS for bleeding problems was 11.7 months. Removals due to premenstrual symptoms were 14; mood swings/depression 13; loss of libido 5; headaches/migraine 9; and acne 7, at 5 years. There were 96 women lost to follow-up at 5 years.[244] [EL = 3]

A Finnish cross-sectional survey (n = 17 914) reported discontinuation rates of 7%, 13%, 19%, 25% and 35% among LNG-IUS users at 1, 2, 3, 4 and 5 years, respectively. There was a significant association between bleeding problems and the premature removal of LNG-IUS (RR 2.77; 95% CI 2.51 to 3.07). Removal was significantly lower in women who had an occasional or total absence of menstruation (RR 0.46; 95% CI 0.43 to 0.50). The relative risk of premature removal of LNG-IUS due to pelvic infection was 1.40 (95% CI 1.25 to 1.57); due to pain 1.32 (95% CI 1.23 to 1.42); depression 1.33 (95% CI 1.24 to 1.43); and due to recurrent vaginal infections 1.25 (95% CI 1.14 to 1.38).[245] [EL = 3]

One non-comparative study (n = 165) in Austria reported a cumulative discontinuation rate of 10% among LNG-IUS users at 3 years. The main reasons for discontinuation were bleeding problems (19%), reduced libido (13%) and other side effects such as skin problems, weight gain, depressive moods and ovarian cysts (31%).[81] [EL = 3] Another non-comparative study (n = 203) in France reported a cumulative discontinuation rate of 11% among LNG-IUS users at 1 year. The main reasons for discontinuation were bleeding problems (48%), pain (22%) and hormonal side effects (13%).[246] [EL = 3]

SUMMARY OF EVIDENCE

Table 5.3 LNG-IUS versus copper IUDs: cumulative discontinuation rates

Reason for removal	Study	Cumulative discontinuation rate (%)			Measurement point (year)	EL
		TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
Overall	154,155		17	20	1	1+
			41	43	3	
			56	53	5	
	149–151		14	16	1	1+
			28	33	2	
			50	45	5	
	143–145	18		24	1	1+
		41		51	3	
		60		67	5	
		72		77	7	
	244			30	1	3
				51	3	
				60	5	
	245			7	1	3
				19	3	
				35	5	
Amenorrhoea	154,155		0.0	1.5	1	1+
			0.0	3.6	3	
			0.0	4.3	5	
	149–151		0.0	2.6	1	1+
			0.0	10.7	2	
			0.0	13.0	5	
	143–145	0.1		4.9	1	1+
		0.2		8.4	2	
		0.4		19.7	5	
		1.1		24.6	7	
	132,133	0.5		23.5	6–7	1+
	244			3.8	5	3
Bleeding and pain	154,155		7.3	7.4	1	1+
			15.3	13	3	
			20.4	15.1	5	
	149–151		3.5	6.5	1	1+
			7.1	7.5	2	
			21.7	8.3	5	
	143–145	7.0		6.0	1	1+
		11.3		8.6	2	
		23.0		15.4	5	
		30.0		20.4	7	
	132,133	11.0		36.0	6–7	1+
	244			10.5	1	3
				13.7	3	
				16.7	5	

Table 5.3 LNG-IUS versus copper IUDs: cumulative discontinuation rates (continued)

Reason for removal	Study	Cumulative discontinuation rate (%)			Measurement point (year)	EL
		TCu 380A (licensed 8 years)	Nova-T 200 (not licensed)	LNG-IUS (licensed 5 years)		
PID	154,155		0.4 1.5 1.6	0.3 0.5 0.6	1 3 5	1+
	143–145	0.8 1.2 1.5		0.9 1.4 1.6	1–2 3–5 6–7	1+
	132,133	0.1		0.3	6–7	1+
	244			0.9 1.2 1.2	1 3 5	3

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

RECOMMENDATION

Healthcare professionals should be aware that:

- up to 60% of women stop using the IUS within 5 years
- the most common reasons for discontinuation are unacceptable vaginal bleeding and pain
- a less common reason for discontinuation is hormonal (non-bleeding) problems.

C

5.5 Adverse effects

Bleeding problems

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported that LNG-IUS (n = 1125) users were more likely to experience amenorrhoea than TCu 380A IUD users (n = 1121) at 3 months (RR 2.15; 95% CI 1.31 to 3.56) and at 3 years (RR 7.24; 95% CI 4.14 to 12.65). No significant differences were noticed between the two groups in terms of prolonged bleeding at 3 months and 1 year. For LNG-IUS users, amenorrhoea, spotting, menorrhagia, dysmenorrhoea and premenstrual syndrome all occurred at a significantly higher incidence in the first 2 years after insertion than at 3 and 4 years. The incidence of these bleeding disturbances declined further at 6 years and later years. Women aged 30 or over using LNG-IUS were significantly less likely to complain of amenorrhoea, scanty bleeding and dysmenorrhoea than were younger women.[142] [EL = 1+]

One European multicentre RCT which compared IUS (n = 1821) and Nova-T 200 IUD (n = 937) reported that 16.8% of LNG-IUS users and 2.7% of Nova-T 200 users experienced a period of at least 90 days' amenorrhoea at 1 year.[152–155] [EL = 1+]

Re-analyses of menstrual diaries (n = 287) from one RCT[153] investigated bleeding patterns in women with post-abortal and post-menstrual insertion of Nova-T 200 IUD and the LNG-IUS. Women having the LNG-IUS inserted post-abortally reported fewer bleeding days than women receiving it post-menstrually. Nova-T 200 IUD users had more bleeding days than LNG-IUS

users. The removal of the superficial endometrium during abortion may result in these improved bleeding patterns.[158] [EL = 1+]

One non-comparative study (n = 165) in Austria reported that cessation of menstruation occurred in 47% of women, over 80% of whom considered this to be a positive change.[81] [EL = 3]

SUMMARY OF EVIDENCE

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

Management of bleeding problems

We did not identify any studies which assessed the management of bleeding problems in LNG-IUS users. However, contraceptive counselling prior to IUS insertion to provide information about the possibility of amenorrhoea may be beneficial in improving user satisfaction and in reducing discontinuation.[68] [EL = 3] (See section 3.5.)

RECOMMENDATION

Women should be informed that:

- irregular bleeding and spotting are common during the first 6 months following IUS insertion
- oligomenorrhoea or amenorrhoea is likely by the end of the first year of IUS use.

C

5.6 Common concerns and symptoms

Weight change

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

One European RCT reported no evidence of a difference in body weight change among women using the copper-releasing Nova-T 200 IUD (n = 937) or the hormone-releasing LNG-IUS (n = 1821). In this study, the mean weight at baseline was 61.6 (SD 10.6) kg in the Nova-T 200 group and 62.0 (SD 10.0) kg in the LNG-IUS group. The mean weight had increased to 64.4 kg in both groups at 5 years (a mean increase of 2.5 kg in the Nova-T 200 group versus 2.4 kg in the LNG-IUS group). Removal of the device due to weight gain was, however, significantly different between LNG-IUS (1.5%) and IUD users (0%).[153] [EL = 1+]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a significant difference in subjective reporting of weight gain (0.7% in the LNG-IUS group versus 0.4% in the IUD group), but no difference in the discontinuation rates due to weight gain or weight loss over the 7 years.[142] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported 16 removals of IUS due to weight gain at 5 years.[244] [EL = 3]

SUMMARY OF EVIDENCE

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

RECOMMENDATION

Women should be informed that there is no evidence that IUS use causes weight gain.

C

Altered mood and libido

The experience of sexual dysfunction, such as loss of libido, is common among young women, ranging from 5–10% in one literature review[169] to about 30% in a national survey in the USA.[170]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a significant cumulative discontinuation rate due to depression of 2.9% versus 0% among LNG-IUS users and Nova-T 200 users, respectively, at 5 years. It was not clear if the occurrence of depression was subjectively reported by the women or objectively measured by the investigators.[153] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported 14 and 13 removals due to premenstrual symptoms and mood swings/depression, respectively, at 5 years. There were 96 women lost to follow-up at 5 years.[244] [EL = 3]

SUMMARY OF EVIDENCE

- Altered mood and libido were not increased in users of LNG-IUS compared with users of the IUD.
- One RCT showed a higher rate of discontinuation of IUS than IUD due to depression at 5 years.

RECOMMENDATION

Women should be informed that any changes in mood and libido are similar whether using the IUS or IUDs, and that the changes are small. **C**

Acne

Skin conditions, particularly acne, are common among young women. Progestogen-only contraceptives, particularly the more androgenic progestogens such as LNG, tend to increase sebum production which makes the skin greasier and prone to acne.[247]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a significant difference in the occurrence of acne (1.0% in the LNG-IUS group versus 0.5% in the TCu 380A IUD group) but discontinuation due to acne was not significant (0.1% versus 0.0%)[142] [EL = 1+]

One European RCT comparing LNG-IUS with Nova-T 200 IUD reported a non-significant cumulative discontinuation rate due to acne of 2.3% versus 0.4%, at 5 years (RR 5.56; 95% CI 0.73 to 42.35). However, a subjective reported side effect of acne was significantly higher among LNG-IUS users (3.5% versus 0.4%) at 3 months and was not significantly different between the two groups at 5 years (1.8% versus 0.3%).[153] [EL = 1+].

One UK non-comparative study (n = 678) reported seven removals due to acne among LNG-IUS users at 5 years. There were 96 women lost to follow-up at 5 years.[244] [EL = 3]

SUMMARY OF EVIDENCE

- In a European RCT, discontinuation due to reported acne was 5 times higher among IUS users than IUD users at 5 years but this did not reach statistical significance. There was initial increased subjective reporting of acne, which was not noted at 5 years.
- Data from one RCT showed a significant increase in acne in the LNG-IUS group, but the discontinuation rate due to acne was not significant between the two groups.

RECOMMENDATION

Women should be informed that there may be an increased likelihood of developing acne as a result of absorption of progestogen, but few women discontinue IUS use for this reason. **C**

Headache and migraines

Headache is one of the most common symptoms experienced in the general population, both in young people and in adults. About 70% of adults report headache in the previous 3 months; the prevalence is greater in females than in males.[248]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a statistically significant difference in the occurrence of headache (8.3% in the LNG-IUS group versus 4.3% in the TCu 380A IUD group) at 7 years.[142] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported nine removals due to headaches/migraine at 5 years. There were 96 women lost to follow-up at 5 years.[244] [EL = 3]

In the current WHO-MEC recommendations, the LNG-IUS is assigned to category '2' for initiation and category '3' for continuation in women who have migraine with focal symptoms at any age. Any new headaches or marked changes in headaches should be evaluated.[63] [EL = 1–4]

SUMMARY OF EVIDENCE

- Headache incidence increases with LNG-IUS use.

RECOMMENDATION

Healthcare professionals should be aware that all progestogen-only methods, including the IUS, may be used by women who have migraine with or without aura. D(GPP)

5.7 Risks

Cardiovascular disease

We did not identify any studies which assessed the risks of cardiovascular disease associated with the use of LNG-IUS.

In the current WHO-MEC recommendations, IUS are assigned to category '2' for women with valvular heart disease. WHO-MEC recommends that prophylactic antibiotics be used at the time of insertion to prevent endocarditis.[63]

A small study identified transient bacteraemia from vaginal organisms in 13% of women within 10 minutes of IUD replacement/insertion.[173] [EL = 3]

In the current WHO-MEC recommendations, LNG-IUS is assigned to category '2' for women with a history of deep vein thrombosis and pulmonary embolism and category '3' for women with current deep vein thrombosis and pulmonary embolism.[63] [EL = 1–4]

RECOMMENDATIONS

Women with a history of venous thromboembolism (VTE) may use the IUS. D(GPP)

Women who have a current VTE and need hormonal contraception while having treatment for the VTE should be referred to a specialist in contraceptive care. D(GPP)

IUS is medically safe for women to use if oestrogen is contraindicated. D(GPP)

Bone mineral density

We did not identify any studies which assessed the effect of LNG-IUS on bone mineral density.

Ectopic pregnancy

An ectopic pregnancy refers to any pregnancy that occurs outside the uterus. The absolute risk of ectopic pregnancy (i.e. the risk that a woman will experience an ectopic pregnancy) is a function of the absolute risk of pregnancy in combination with the conditional risk of ectopic pregnancy (i.e. the risk that a pregnancy will be ectopic). All methods of contraception decrease the risk of ectopic pregnancy as they reduce the absolute risk of pregnancy. We did not identify any studies which compared the risk of ectopic pregnancy in IUS users and non-contraceptors. The **relative** likelihood of a pregnancy being ectopic is greatly increased when a woman becomes pregnant during use of an intrauterine device.[174] It is estimated that 1.4 per 100

pregnancies in women using no contraception is likely to be an ectopic pregnancy. The ectopic pregnancy rate in women generally increases with age.

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported 0 versus 2 ectopic pregnancies in LNG-IUS and TCu 380A users, respectively), at 7 years.[142] [EL = 1+]

One European multicentre RCT compared IUS (n = 1821) and Nova-T 200 IUD (n = 937). The ectopic pregnancy rates were 0.02% versus 0.25% in the IUS and Nova-T 200 groups, respectively, during the 5 year period.[153] [EL = 1+]

Interim results from the WHO international muticentre RCT (n = 3815 insertions) reported a significant difference in ectopic pregnancy rate between LNG-IUS and TCu 380A IUD users at and after 6 years (0.0% versus 0.1%).[132,133] [EL = 1+] However, the rates were very low.

A cross-sectional survey of 17 360 users of LNG-IUS reported the outcome of pregnancy during LNG-IUS use. One hundred and thirty-two pregnancies were reported and 108 medical records were reviewed. In 64 pregnancies, conception occurred with the LNG-IUS *in situ*. Thirty-three pregnancies were ectopic.[249] [EL = 3]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported one ectopic pregnancy at 5 years.[244] [EL = 3]

The LNG-IUS is assigned to category '1' for women with past ectopic pregnancy in the current WHO-MEC recommendations. When a woman becomes pregnant during intrauterine device use, the relative likelihood of ectopic pregnancy is increased.[63] [EL = 4]

SUMMARY OF EVIDENCE

- Ectopic pregnancy rates from 0% to 0.1% were reported in users of LNG-IUS.
- LNG-IUS users have lower ectopic pregnancy rates than IUD users but this not clinically significant.

RECOMMENDATIONS

Women should be informed that the risk of ectopic pregnancy when using the IUS is lower than when using no contraception. **D**

Women should be informed that the overall risk of ectopic pregnancy when using the IUS is very low, at about 1 in 1000 in 5 years. **D(GPP)**

If a woman becomes pregnant with the IUS *in situ*, the risk of ectopic pregnancy is about 1 in 20, and she should seek advice to exclude ectopic pregnancy. **D(GPP)**

Actinomyces-like organisms

Actinomyces israelii are commensal bacteria of the female genital tract.

Actinomyces-like organisms (ALOs) are found in women with and without an IUD.[178–181] The role of ALOs in IUD users is unclear.[182] They may be identified on cervical smears, but have not been shown to be predictive of any disease.[121,183–185] IUDs users may have a higher risk of infection with ALOs compared with non-users.

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported a similarly low incidence of ALOs on cervical smears (0.0% versus 0.1%) in both the LNG-IUS and the TCu 380A IUD groups.[142] [EL = 1–]

A Swiss study of 156 women found the incidence of ALOs to be significantly higher among women using Multiload Cu375 than among women using LNG-IUS (20% versus 2.9% at 22 months of follow-up).[187] [EL = 3] However, differences between the prevalence rates may be attributable to cervical sampling and staining techniques, population characteristics and the potential for bias associated with retrospective reviews of case notes.

RECOMMENDATION

The presence of *Actinomyces*-like organisms on a cervical smear in a woman with a current IUS requires an assessment to exclude pelvic infection. Routine removal is not indicated in women without signs of pelvic infection. **D(GPP)**

Pelvic inflammatory disease

A major cause of pelvic inflammatory disease (PID) is *Chlamydia trachomatis*, a sexually transmitted infection of the genital tract. PID results in chronic abdominal pain, ectopic pregnancy and can lead to tubal factor infertility.[189] *Chlamydia trachomatis* is the most common STI in the UK and Europe, present in 11% of the sexually active population aged 19 or younger.[190] [EL = 3] Asymptomatic chlamydial infection can only be detected by screening. Uterine instrumentation carried out as part of insertion may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic PID. The Chief Medical Officer's Advisory Group on *Chlamydia trachomatis* recommends that opportunistic screening of any woman undergoing instrumentation of the uterus be considered because of a resultant risk of ascending infection.[191] [EL = 4]

The annual incidence of PID is estimated to be 1–2% in women of reproductive age in the USA.[192]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported no significant differences between LNG-IUS users and TCu 380A users in discontinuation rates due to PID (0.9% versus 0.8% ,1.4% versus 1.2% and 1.6% versus 1.5% at 1–2, 3–5 and 6–7 years, respectively).[142–146] [EL = 1+]

One European multicentre RCT which compared IUS (n = 1821) and Nova-T 200 IUD (n = 937) reported cumulative rates for removal due to PID were 0.3% versus 0.4%, 0.5% versus 1.0%, 0.5% versus 1.5%, 0.5% versus 1.5% and 0.6% versus 1.6% at 1, 2, 3, 4 and 5 years, respectively.[152–155] [EL = 1+]

Interim results from the WHO international multicentre RCT (n = 3815 insertions) showed no significant difference in discontinuation rates due to PID between LNG-IUS users (n = 464) and TCu 380A IUD users (n = 580) at and after 6 years (0.3% versus 0.1%).[132] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported cumulative discontinuation rates due to PID of 0.9%, 1.2%, 1.2%, 1.2% and 1.2% at 1, 2, 3, 4 and 5 years, respectively.[244] [EL = 3]

In the current WHO-MEC recommendations, LNG-IUS is assigned to category '1' for initiation and continuation in women with past PID with subsequent pregnancy, category '2' for initiation and continuation in women with past PID without subsequent pregnancy, and category '4' for initiation in women with current PID.[63] [EL = 1–4]

SUMMARY OF EVIDENCE

- The risk of PID in IUS users is low.
- Removal due to PID among IUS users is below 1% at 1 year , and below 1.5% at 5 years.

RECOMMENDATION

Women should be informed that the risk of developing pelvic inflammatory disease following IUS insertion is very low (less than 1 in 100) in women who are at low risk of STIs. **C**

Uterine perforation

Uterine perforation occurs in fewer than 1 in 1000 insertions of IUDs.[119,199]

One multinational RCT (n = 2246 women in Singapore, Brazil, Egypt and the USA) reported similarly low discontinuation rates due to uterine perforation (0.1% versus 0.0%) and cervical perforation (0% versus < 0.1%) between LNG-IUS users and TCu 380A users at 7 years.[142] [EL = 1+]

One UK non-comparative study (n = 678) undertaken to determine the performance of LNG-IUS reported no perforation after 5 years of use.[244] [EL = 3]

Another non-comparative study (n = 3452) reported three uterine perforations with LNG-IUS (0.9 per 1000 insertions) at 3 years.[250] [EL = 3]

SUMMARY OF EVIDENCE

- The risk of uterine perforation associated with IUD and LNG-IUS use is low: less than 0.1%.

RECOMMENDATIONS

Women should be informed that the risk of uterine perforation at the time of IUS insertion is very low (less than 1 in 1000). **D**

Women should be informed about symptoms of uterine perforation or infection which would warrant an early review of IUS use. **D(GPP)**

Contraceptive care providers should be aware that the risk of perforation is related to the skill of the healthcare professional inserting the IUS. **D(GPP)**

Women who become pregnant while using the IUS

We did not identify any studies assessing the management of women who become pregnant while using the IUS. However, the UKSPR comments that if the pregnancy continues, there may be added risks to the fetus due to the hormonal exposure. (Refer to the recommendations on ectopic pregnancy earlier in this section.)

RECOMMENDATIONS

Women with an intrauterine pregnancy with an IUS *in situ*, should be advised to have the IUS removed before 12 completed weeks' gestation whether or not they intend to continue the pregnancy. **D(GPP)**

5.8 Return to fertility

A multinational European RCT compared the recovery of fertility between ex-users of LNG-IUS (n = 139) and Nova-T 200 IUD (n = 71). There was no significant difference in cumulative conception rates between ex-LNG-IUS users and ex-Nova-T 200 users (79.1% versus 71.2% at 1 year and 86.6% versus 79.7% at 2 years). Ninety-six percent of the pregnancies occurred during the first year after removal and 84% of the pregnancies in the Nova-T 200 group and 86% in the LNG-IUS group ended in live births.[155] [EL = 1+]

Another RCT reported a pregnancy rate of 96.4% in ex-LNG-IUS users (n = 60) compared with 91.1% in ex-TCu 380A IUD users (n = 50) at 1 year.[147,208] [EL = 1+]

A cohort study comparing pregnancy rates after cessation of use of LNG-IUS (n = 91), TCu 380A (n = 103) and Norplant (n = 62) reported pregnancy rates of 88%, 88% and 87% in these three groups, respectively, at 2 years. For all groups, pregnancy rates were higher in women under 30 years of age.[251] [EL = 2]

A questionnaire survey of pregnant women (n = 2841) in the UK evaluated the impact of contraceptive method on subsequent fecundity. It reported that all LNG-IUS users (n = 13) conceived within 1 month after discontinuation.[209] [EL = 3] (See Sections 4.8, 6.7 and 7.7.)

SUMMARY OF EVIDENCE

- Between 79% and 96% of women had achieved conception by 1 year after removal of LNG-IUS.

RECOMMENDATION

Women should be informed that there is no evidence of a delay in the return of fertility following removal or expulsion of the IUS. **C**

5.9 Details of method use

Assessment prior to insertion

(See Section 3.6.)

All women considering the use of LNG-IUS should be assessed as outlined for the IUD.[201] This includes bimanual pelvic examination, testing for STIs if indicated, measurement of pulse and blood pressure, prophylaxis to prevent pelvic infection if indicated, and prophylaxis to prevent bacterial endocarditis in those at risk. Women with an identified risk of STI should have their decision on their chosen method of contraception reviewed and alternative methods should be discussed.

WHO-MEC recommends that LNG-IUS should not be inserted when a woman has PID, or an STI, currently or within the last 3 months.[63] The FFPRHC recommends that, as for IUD insertion, after considering other contraceptive methods, a woman may use the LNG-IUS within 3 months of treated pelvic infection, provided she has no signs and symptoms.[201]

RECOMMENDATIONS

Testing for the following should be undertaken before IUS insertion: **D(GPP)**

- *Chlamydia trachomatis* in women at risk of STIs
- *Neisseria gonorrhoeae* in women from areas where the disease is prevalent and who are at risk of STIs
- any STIs in women who request it.

If testing for STIs is not possible, or has not been completed, prophylactic antibiotics should be used before IUS insertion in women at increased risks of STIs. **D(GPP)**

Women with identified risks associated with uterine or systemic infection should have investigations, and appropriate prophylaxis or treatment before insertion of the IUS. **D(GPP)**

Information prior to insertion

(See Section 3.5.)

RECOMMENDATIONS

Women should be informed about failure rates, benefits, risks and side effects of the IUS. **D(GPP)**

Women should be informed that insertion of an IUS may cause pain and discomfort for a few hours and light bleeding for a few days, and they should be informed about appropriate pain relief. **D(GPP)**

Position within the uterine cavity

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

Time of insertion of the LNG-IUS

In a normal menstrual cycle

It is important to check that the woman is not pregnant before insertion by taking a menstrual and coital history, and carrying out a pregnancy test if indicated. The Summary of Product

Characteristics (SPC) for the LNG-IUS recommends insertion within 7 days of the onset of menstruation (at any time if a replacement) or immediately after a first-trimester abortion. The FFPRHC recommends that an LNG-IUS can be inserted at other times in the cycle if there has been no risk of pregnancy. In such situations additional contraception is required for 7 days.[252]

When switching method

The UKSPR and the FFPRHC both recommend that the LNG-IUS can be inserted at any time if it is reasonably certain that the woman is not pregnant and other hormonal methods have been used consistently and correctly. Additional contraceptive protection is then required for the next 7 days.[252] [EL = 1–4]

Following abortion

WHO-MEC recommends the LNG-IUS be inserted immediately after surgical abortion – first-trimester or second-trimester.[174] After medical abortion, the insertion of the LNG-IUS can be performed at any time after the procedure is complete.[252]

One RCT compared LNG-IUS with Nova-T 200 IUD inserted at the time of elective abortion. It reported significantly lower cumulative pregnancy rates (0.8% versus 9.5%) but significantly higher cumulative discontinuation rates in LNG-IUS users due to hormonal reasons (15.9% versus 3.9%) at 5 years.[211] [EL = 1+]

The RCOG abortion guideline recommends that intrauterine contraception can be inserted immediately following a first- or second-trimester abortion.[215] [EL = 1–4]

Post delivery

Advice regarding postpartum insertion of the LNG-IUS follows that for the IUD.[201] LNG-IUS is assigned to category '1' for insertion at 4 or more weeks postpartum.[63] [EL = 1–4]

RECOMMENDATIONS

Healthcare professionals should be aware that, provided that it is reasonably certain that the woman is not pregnant, the IUS can be inserted:

D(GPP)

- at any time during the menstrual cycle (if the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be used for the first 7 days following insertion)
- immediately after first- or second-trimester abortion, or at any time thereafter
- from 4 weeks post partum, irrespective of the mode of delivery.*

5.10 Training of healthcare professionals

(See Section 3.14.)

We did not identify any studies assessing the training of healthcare professionals in the insertion of IUS. Advice regarding training follows that for IUDs.

A large prospective study, which included 17 469 Multiload Cu375 insertions by 1699 doctors, reported an incidence of 1.6 uterine perforation per 1000 insertions at 6 years. Doctors who performed fewer than 10 IUD insertions in the 6 year period reported significantly more perforations than doctors who performed from10 to 49 IUD insertions (RR 2.3; 95% CI 0.99 to 5.26) and doctors who performed from 50 to 99 IUD insertions (RR 7.3; 95% CI 0.94 to 56.3) in the same study period.[199] [EL = 3]

* At the time of publication (October 2005), use before 6 weeks postpartum was outside the UK marketing authorisation for the IUS. 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.

A secondary analysis of TCu 380A acceptors from one RCT in three developing countries compared insertion failures and complications between non-physician (n = 174) and physician insertions (n = 193). It reported an overall significantly higher cumulative discontinuation rate due to expulsion (8.6% versus 2.7%), bleeding/pain (8.1% versus 1.4%) in the non-physician insertion group. The overall continuation rate was also lower (77.3% versus 85.5%) in this group at 12 months. This suggested that appropriate competency-based training is required by non-physicians to limit the number of expulsions and removals for bleeding and pain.[220] [EL = 2+]

A cohort study compared IUD insertions by specialist nurses (n = 22) and doctors (n = 28). It reported that adequately trained nurses were proficient and safe at IUD insertions, regardless of the woman's parity.[221] [EL = 2–]

It has been suggested that the performance of IUDs in comparative trials is often reflective of operator skills and quality of care and follow-up, rather than the nature of the device studied.[141] [EL = 1++][222] [EL = 4] IUD expulsion rates were reported to be significantly higher for inexperienced inserters.[223] [EL = 1+]

The FFPRHC has specific training requirements for healthcare professionals wishing to obtain a letter of competence (LoC) in intrauterine techniques (IUT). Competence in gynaecological examination and the assessment, management and investigation of women with IUD problems are required for all healthcare professionals inserting IUDs. Recertification should ensure continuing competence. The LoC must be updated every 5 years, with at least 2 hours of relevant continuing education and a log of at least 12 insertions in 12 months or six in 6 months using at least two different types of device in unanaesthetised patients.

The Royal College of Nursing Sexual Health Forum has issued training guidance and requirements for nurses wishing to insert IUDs.[107] [EL = 4] It outlines eligibility criteria for adequate training (for example, obtain a recognised family planning/contraception qualification) and the knowledge and skills required to perform insertion and explain various aspects of care. Nurses can receive training from experienced doctors with a letter of competence in intrauterine techniques (LoC IUT). Nurses must also observe a minimum of five insertions, and fit a minimum of ten devices of varying types.

RECOMMENDATION

The IUS should only be fitted by trained personnel with continuing experience of inserting at least one IUD or one IUS a month. **C**

5.11 Specific groups

Adolescents

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

One RCT (n = 200) compared LNG-IUS and COC use among young nulliparous women aged 18–25 years. It reported no pregnancies or PID in either group at 1 year. There was one partial expulsion in the IUS group at 6 months. The discontinuation rates due to pain were 6.7% versus 0%; due to bleeding 2.5% versus 0%; and due to spotting 0% versus 1.25%. The overall discontinuation rate was 20% versus 27% at 1 year.[253] [EL = 1+]

LNG-IUS is assigned to category '2' for women under 20 years.[63] However, WHO-MEC comments that there is concern about both the risk of expulsion due to nulliparity and the risk of STIs due to patterns of sexual behaviour in younger age groups.

Women over 40 years of age

A non-comparative study (n = 203) in France reported no pregnancy, expulsion or perforation among LNG-IUS users aged 35–45 years at 1 year. The cumulative discontinuation rate was 11%. The main reasons for discontinuation were bleeding problems (48%), pain (22%) and hormonal side effects (13%) at 1 year.[246] [EL = 3] (Refer to Section 5.1 for use in women aged 45 year or over.)

RECOMMENDATIONS

The IUS may be used by adolescents, but STI risk should be considered where appropriate. D(GPP)

Healthcare professionals should be aware that: D(GPP)

- IUS use is not contraindicated in nulliparous women of any age
- women of all ages may use the IUS.

Women with body mass index over 30 kg/m²

We did not identify any studies which assessed the relationship between body weight and efficacy of the IUS. LNG-IUS is assigned to category '1' for women with BMI > 30kg/m² in the current WHO-MEC recommendations.[63]

Women who are breastfeeding

A cross-sectional study (n = 11) reported low concentrations of LNG in breast milk in breastfeeding women using the IUS.[254] [EL = 3] It has been recommended that women who are breastfeeding and who are 4 or more weeks postpartum may choose the LNG-IUS.[252] In the current WHO-MEC recommendations, LNG-IUS is assigned to category '1' for women who are beyond 4 weeks postpartum and breastfeeding.[63]

RECOMMENDATION

Healthcare professionals should be aware that the IUS can safely be used by women who are breastfeeding. D

5.12 Medical conditions and contraindications

Diabetes

One RCT compared the effect of IUS use (n = 29) or IUD use (n = 30) on glucose metabolism among women with uncomplicated insulin-dependent diabetes mellitus and reported no significant differences in mean glycosylated levels, fasting-serum glucose levels and daily insulin doses between the two groups at 6 and 12 months, suggesting that both the IUD and IUS are safe contraceptive methods for women with diabetes.[229] [EL = 1+]

LNG-IUS is assigned to category '2' for women with non-insulin-dependent and insulin-dependent diabetes in the current WHO-MEC recommendations. Whether the amount of LNG released may influence carbohydrate and lipid metabolism is not clear.[63]

Epilepsy

There is no evidence that the medical condition of a woman with epilepsy is altered by the presence of an LNG-IUS. However, there may be increased risk of a fit being precipitated during the insertion procedure.

LNG-IUS is assigned to category '1' for women with epilepsy in the current WHO-MEC recommendations.[63]

Sexually transmitted infections, HIV and AIDS

(See Section 3.11.)

We did not identify any studies which addressed the use of LNG-IUS in women with HIV/AIDS. (See Chapter 4.)

In the current WHO-MEC recommendations, LNG-IUS is assigned to category '2' for initiation and continuation for women who are at high risk of HIV or who are HIV-infected. For women with AIDS, LNG-IUS is assigned to category '3' for initiation and category '2' for continuation. For women who are clinically well on antiretroviral therapy, LNG-IUS is assigned to category '2' for both initiation and continuation.[63]

SUMMARY OF EVIDENCE

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

RECOMMENDATION

Healthcare professionals should be aware that: D(GPP)

- IUS use is not contraindicated in women with diabetes
- emergency drugs including anti-epileptic medication should be available at the time of IUS insertion in a woman with epilepsy because there may be an increased risk of a seizure at the time of cervical dilation
- IUS is a safe and effective method of contraception for women who are HIV-positive or have AIDS (safer sex using condoms should be encouraged in this group).

5.13 Drug interactions

Data from an ongoing survey have not identified any reduction in the efficacy of LNG-IUS with liver enzyme-inducing drugs.[255] [EL = 3] In the current WHO-MEC recommendations, LNG-IUS is assigned to category '1' for women who are prescribed drugs which affect liver enzymes, such as rifampicin and anti-epileptic drugs.[63]

Levonorgestrel is released directly into the uterine cavity with LNG-IUS, and contraceptive effects are mainly local and, therefore, not affected by the presence or absence of enzyme-inducing epileptic medication.[256] [EL = 2–3]

Antibiotics

In the current WHO-MEC recommendations, LNG-IUS is assigned to category '1' for women who are prescribed antibiotics.[63]

RECOMMENDATION

Healthcare professionals should be aware that there is no evidence that the effectiveness of the IUS is reduced when taking any other medication. D

5.14 Follow-up

The UKSPR recommends a follow-up visit 3–6 weeks after insertion for IUD users.[79] [EL = 1–4]

RECOMMENDATION

A follow-up visit should be recommended after the first menses, or 3–6 weeks after insertion, to exclude infection, perforation or expulsion. Thereafter, a woman should be strongly encouraged to return at any time to discuss problems, if she wants to change her method of contraception, or if it is time to have the IUS removed. D(GPP)

6. Progestogen-only injectable contraceptives (POICs)

6.1 Introduction

What they are

Progestogen-only injectable contraceptives (POICs) are slow-release preparations lasting 2 or 3 months. Depot medroxyprogesterone acetate (DMPA) and norethisterone enantate (NET-EN) are the two POICs available in the UK. DMPA is licensed as a first-line contraceptive for long-term and short-term use. NET-EN is licensed for short-term use (up to two injections) by women whose partners undergo vasectomy, until the vasectomy is effective, and by women immunised against rubella, to prevent pregnancy until immunity develops.

Slow release of the drug from the surface of the DMPA microcrystals provides a subsequent prolonged action. Injection of NET-EN in its castor oil/benzyl benzoate vehicle is followed by partial hydrolysis of the ester to the active compound norethisterone.[257]

DMPA is an aqueous suspension available in a pre-filled syringe which should be thoroughly mixed before use to ensure complete suspension of the contents. NET-EN is a thick oily fluid which is drawn up into a syringe; the ampoule should be immersed in warm water before use to reduce the viscosity. Both preparations are given by intramuscular injection: DMPA at a dose of 150 mg (in 1 ml) every 12 weeks and NET-EN at a dose of 200 mg (in 1 ml) every 8 weeks. With each there is a sharp rise in progestogen blood concentration over one to two days, followed by a gradual decline over the following weeks. A new micronised formulation of DMPA has been developed, to be given subcutaneously every 12 weeks. While delivering a 30% lower total dose (104 mg) than the intramuscular formulation, the subcutaneous formulation suppressed ovulation for more than 13 weeks in all subjects and was not affected by body mass.[258]

Mechanism of action

Both DMPA and NET-EN prevent pregnancy by the inhibition of ovulation and thickening the cervical mucus, thereby presenting a barrier for sperm penetration. In addition, changes to the endometrium make it an unfavourable environment for implantation.[259–262] [EL = 3]

RECOMMENDATION

Women should be informed that progestogen-only contraceptive injectables act primarily by preventing ovulation. **C**

Use in Great Britain

In 2003/04, it was estimated that fewer than 3% of women aged 16–49 years in Great Britain use the injectables as their method of contraception.[1] [EL = 3]

Duration of action

The ideal administration interval with NET-EN has been found to be 56 ± 7 days.[263] Longer intervals between NET-EN administrations are associated with higher pregnancy rates. Four pregnancies occurred in one study using 70 ± 7 days as the administration interval over 33 months. Another, administering NET-EN every 12 weeks over a 12 month period, resulted in a pregnancy rate of 0.1% to 0.6%.[259]

With POICs, progestogen blood concentrations remain consistently high enough to maintain contraceptive effect for 3 months post-injection with DMPA and for 2 months with NET-EN.[264–266]

The time it takes for progestogen concentrations to be insufficient for contraception (i.e. to wear off) may vary from population to population.[267] [EL = 3]

RECOMMENDATION

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

The evidence

Considering how widely used DMPA is worldwide, there is little published evidence of its safety, effectiveness and associated discontinuation rates. Asian and South American studies on weight changes have not been cited here as the average weight of these populations is so different to the UK. (See Section 3.4.)

6.2 Effectiveness

In a multinational RCT that compared DMPA (n = 1587) with NET-EN (n = 789), given at their licensed dosage intervals, the reported cumulative pregnancy rates were 0.1% versus 0.4% at 1 year, and 0.4% in both groups at 2 years.[268] [EL = 1+] For DMPA, these effectiveness rates have been confirmed in one multinational RCT (0.7% at 1 year)[269] [EL = 1+] and one cohort study (0.4% at 1 year), in which DMPA was given at the licensed interval with NET-EN given every 12 weeks.[270] [EL = 2+]

A cohort study in Kenya (n = 1076) reported a pregnancy rate of 1.5% in TCu 380A users, 2.1% in users of a COC, and 0.3% in DMPA users at 1 year.[156] [EL = 2+]

A US cohort study of adolescents living in inner cities reported a cumulative pregnancy rate of 11% in DMPA users (n = 111) versus 28% in COC users (n = 50) at 1 year.[271] [EL = 2–]

RECOMMENDATION

Women should be informed that the pregnancy rate associated with injectable contraceptives, when given at the recommended intervals, is very low (fewer than 4 in 1000 over 2 years) and that the pregnancy rate with depot medroxyprogesterone acetate (DMPA) is lower than that with norethisterone enantate (NET-EN). **C**

6.3 Discontinuation and reasons for discontinuation

(See Section 3.10.)

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. The cumulative discontinuation rate was 41% in both groups at 1 year, mainly due to bleeding problems (rates varied between centres, ranging from 0% to 22%).[272] [EL = 1–]

* At the time of publication (October 2005), NET-EN was not licensed for long-term use. 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.

Four non-comparative studies from the USA demonstrated discontinuation rates among DMPA users ranging from 41% to 77% at 1 year. One study showed cumulative discontinuation rates up to 79% among DMPA users at 5 years. The main reasons for discontinuation were bleeding problems (8% to 30%) and weight gain (7% to 24%).[273–276] [EL = 3]

Two retrospective surveys conducted in New Zealand and Australia (n = 252 women treated over 5 years, mean number of injections 8.7; n = 363 women treated over 20 years, mean number of injection 6.3) reported discontinuation rates of 20% to 35% for bleeding disturbances and 8% to 12% for weight gain among DMPA users.[277,278] [EL = 3]

A UK non-comparative study (n = 707) reported cumulative discontinuation rates of 23%, 36% and 66% at 1, 2 and 3 years, respectively, among NET-EN users. The main reasons for discontinuation were unacceptable menstrual bleeding (39%) and other method-related side effects (25%).[263] [EL = 3]

One multinational RCT reported similar cumulative discontinuation rates among DMPA (n = 1587) and NET-EN (n = 789) users (51% versus 50% at 1 year, and 74% versus 71% at 2 years). Apart from discontinuation for personal reasons (40%), the other reasons for discontinuation were around 20% for bleeding problems and 15% to 25% for amenorrhoea at 2 years.[268] [EL = 1+]

A New Zealand cohort study (n = 6262) reported cumulative discontinuation rates of 48%, 44% and 42% among DMPA, IUD and COC users, respectively, at 2 years. Personal reasons or changing to a 'definitive contraceptive method' were more common than medical reasons for discontinuation (28% versus 20% versus 35%). Discontinuations due to medical reasons, which included weight changes and bleeding problems, were 12% versus 16% versus 21%.[279] [EL = 2+]

A US cohort study (n = 122) reported significantly lower discontinuation rates among postpartum adolescents using DMPA than among those using COC (45% versus 73%) at 1 year. The reasons for discontinuation due to disrupted menstrual cycle were 40% versus 4% and due to weight gain 12% versus 0% at 1 year.[280] [EL = 2+]

A cohort study reported similar discontinuation rates among postpartum adolescents using DMPA (n = 111) or COC (n = 50) at 66% versus 68% at 1 year. The primary reason for discontinuation was side effects which included bleeding problems and weight gain (79% versus 44%).[271] [EL = 2–]

An Australian case note review of DMPA discontinuers (n = 247) reported that 42% had no further need for contraception, 10% experienced bleeding irregularities, and 9% desired pregnancy.[277] [EL = 3]

A US cross-sectional survey of adolescent users of DMPA (n = 35) and Norplant (n = 31) reported that the most common reported reasons for discontinuation of DMPA were irregular bleeding (60%), weight gain (40%), increased headaches (26%), mood changes (20%), fatigue (20%) and loss of scalp hair (20%) at 1 year.[281] [EL = 3]

SUMMARY OF EVIDENCE

- The overall discontinuation rate for all reasons among DMPA users is around 50% at 1 year.
- The discontinuation rate due to bleeding problems is between 30% and 40% among DMPA users.

RECOMMENDATION

Healthcare professionals should be aware that:

- up to 50% of women stop using DMPA by 1 year
- the most common reason for discontinuation is an altered bleeding pattern, such as persistent bleeding.

C

6.4 Adverse effects

We did not identify any studies which reported the incidence of anaphylactic reaction or death as a result of receiving DMPA or NET-EN injection.

Bleeding problems

Amenorrhoea is a predictable side effect of DMPA and NET-EN, owing to the inhibition of both ovulation and follicular development. Amenorrhoea may be generally more acceptable to women than prolonged or frequent bleeding.

In one RCT (n = 3172), significantly more DMPA users reported amenorrhoea than NET-EN users (12% versus 7% and 24% versus 15% at 1 and 2 years, respectively). The prevalence of amenorrhoea increases the longer that POICs are used. No significant differences in the incidence of 'bleeding problems' were reported among DMPA and NET-EN users at 1 and 2 years.[268] [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. The most common bleeding problem for both groups was infrequent bleeding. Amenorrhoea was experienced by 9% to 10% of women in the first 3 months and 41% to 47% at 1 year.[272] [EL = 1–]

In a study which assessed the effect of counselling on adherence in DMPA users, amenorrhoea was the major side effect reported, occurring in 34% to 35% of the women.[70] [EL = 3]

SUMMARY OF EVIDENCE

- Bleeding problems occur in around 20% to 40% of DMPA users.

Management of bleeding problems

Amenorrhoea is common in women using DMPA. If unacceptable, an alternative method should be offered.[79] [EL = 4] Fewer than 10% of women experience prolonged and sometimes heavy bleeding. Underlying gynaecological problems should be excluded if an unexpected change in bleeding patterns occurs.

One RCT (n = 278) compared ethinylestradiol, estrone sulphate or a placebo in the treatment of vaginal bleeding (episodes of longer than 7 days) among DMPA users. Treatment success (bleeding stopped for 2 days or more during treatment and had not recurred) was significantly higher in the ethinylestradiol group (93% versus 76% versus 74%) than in the other two groups.[282] [EL = 1+]

One RCT in Thailand evaluated the effect of mefenamic acid on controlling irregular uterine bleeding in DMPA users. A significantly higher number of women stopped bleeding in the group given mefenamic acid (n = 23, mean BMI 22.3 kg/m^2) when compared with the group given placebo (n = 25, mean BMI 22.3) in the first week (69.6% versus 40%). However, there was no significant difference in mean bleeding-free days between the two groups at 4 weeks. This suggested that mefenamic acid was not effective in the long-term control of bleeding during DMPA use.[283] [EL = 1–]

A small RCT in the USA evaluated the effect of mifepristone in the prevention of breakthrough bleeding (BTB) in new starters of DMPA. A significant reduction in the number of days of BTB and the number of cycles with prolonged bleeding intervals was reported in women given mifepristone (n = 10) when compared with women given placebo (n = 10).[284] [EL = 1–]

In a 6 month cohort study of women who were administered DMPA (n = 349) or NET-EN (n = 304) in the puerperium (within 6–12 hours of delivery), no significant differences were identified in the incidence of prolonged (> 21 days) bleeding or in the mean duration of bleeding between groups. In the same study, a subgroup of women was given naproxen or placebo to treat heavy bleeding (n = 48). No significant differences were reported between the groups in the duration or amount of bleeding.[285] [EL = 2–]

Three studies have shown that counselling women about bleeding disturbances reduces discontinuation rates in DMPA users. In two 1 year studies (n = 350 and n = 421) significantly fewer women who received structured counselling discontinued DMPA use both for all reasons

and for reasons related to bleeding patterns when compared with women who received routine counselling. [EL = 1+][70] [EL = 2+][286] (See Section 3.5.)

A survey in Bolivia (n = 352) reported that women advised to return to the clinic if experiencing problems were 2.7 times more likely to continue DMPA at 1 year than those who did not receive such advice. Women advised of the possibility of amenorrhoea were 2.5 times more likely to return for a second injection, whilst those believing regular bleeding to be a requisite for maintaining good health were more likely to discontinue DMPA use.[69] [EL = 3]

SUMMARY OF EVIDENCE

- Ethinylestradiol and mefenamic acid may be effective in the management of bleeding problems associated with DMPA use.
- Counselling about bleeding disturbances associated with DMPA use is beneficial in improving continuation rates.

RECOMMENDATIONS

Women should be informed that amenorrhoea is likely during the use of injectable contraceptives; this is

- more likely with DMPA than NET-EN
- more likely as time goes by
- not harmful.

C

Healthcare professionals should be aware that a pattern of persistent bleeding associated with DMPA use can be treated with mefenamic acid or ethinylestradiol.

C

6.5 Common concerns and symptoms

Weight change

Weight fluctuation in women of reproductive age is common, whether or not hormonal contraceptives are used. Weight increases with age in women of child-bearing age and the proportion of those categorised as overweight increases with each age decade. It is estimated that 25% of women in the UK are categorised as obese.[167] Studies on weight gain during POIC use reported conflicting results. The mechanisms by which contraceptive hormones may affect body weight are not well known.

One multinational RCT reported a mean weight gain of about 3 kg in both DMPA (n = 1587) and NET-EN (n = 789) users at 2 years.[268] [EL = 1+]

A systematic review to update the WHO-MEC guidance identified two relevant studies. A cohort study of adolescent DMPA and COC users (n = 239) reported a significantly greater weight gain among overweight DMPA users (~6.2 kg) compared with both 'normal' weight DMPA users (3.1 kg) and overweight OC users (3.4 kg) at 1 year. This was believed to be due to an appetite-stimulating effect and altered tryptophan metabolism. Overweight women may be at increased risk of weight gain.[287] [EL = 2+]. The other study (n = 885) reported similar weight gain (~2 kg) in DMPA users who weighed more or less than 91 kg at baseline.[288] [EL = 3]

RECOMMENDATION

Women should be informed that DMPA use may be associated with an increase of up to 2–3 kg in weight over 1 year.

C

Altered mood and libido

A US cohort study reported an increased likelihood of depressive symptoms in DMPA users (n = 183) compared with non-users (n = 274) at 3 years (OR 1.44; 95%CI 1.00 to 2.07), although significantly more DMPA users reported symptoms at baseline (28% versus 18%). Women who

discontinued DMPA (62%) also had a greater likelihood of depressive symptoms than non-users (OR 1.60; 95%CI 1.03 to 2.48).[289] [EL = 2–]

Another US cohort study (n = 63) reported no significant differences in mood and depression scores in adolescents (aged 16 to 21 years) who used DMPA, compared with non-users of hormonal contraception at 1 year.[290] [EL = 2–]

One US cohort study of adolescents (n = 199) reported no significant differences in depression between users of DMPA and COC (53% versus 57%) at 6 months.[291] [EL = 2–]

A US cross-sectional survey (n = 495) of users of DMPA reported that the 44% continuing to use the method at 1 year had significantly lower baseline scores for depression than did those who discontinued the method or who were lost to follow-up.[292] [EL = 3]

DMPA is assigned to category '1' for women with selective depressive disorders.[63] [EL = 1–4]

We did not identify any studies which assessed the effect of POICs on libido.

Acne

Acne is a common skin condition affecting 35% to 90% of adolescents.[293] Progestogens, particularly the more androgenic ones such as LNG, are a potent stimulus to sebum secretion which tends to make the skin greasier and prone to acne.[247] DMPA has relatively low androgenic activity.

A US cross-sectional survey of adolescent users of DMPA (n = 35) and Norplant (n = 31) reported no difference in the incidence of acne as a reason for discontinuation (9% of DMPA users and 10% of Norplant users).[281] [EL = 3]

Headache and migraine

Headache is one of the most common symptoms experienced in the general population, both in young people and in adults. About 70% of adults report headache in the previous 3 months; the prevalence is greater in females than in males.[248] The prevalence of migraine has been estimated to be about 7% among adolescents.[294]

A cohort study (n = 199) reported no significant changes from baseline in the occurrence of headaches among COC users or DMPA users at 6 months.[291] [EL = 2–] The figures for discontinuation due to increased headaches in a small US cross-sectional survey of adolescent users of DMPA and Norplant were similar (26% versus 35%).[281] [EL = 3]

RECOMMENDATIONS

Healthcare professionals should be aware that the use of DMPA is not associated with acne, depression or headaches. **C**

Healthcare professionals should be aware that all progestogen-only methods, including injectable contraceptives, may be used by women who have migraine with or without aura. **D(GPP)**

6.6 Risks

Cardiovascular disease

Lipid profiles are considered a surrogate marker for cardiovascular risk. Low high-density lipoprotein (HDL) levels and high low-density lipoprotein (LDL) levels are independent risk factors for the development of atherosclerosis and cardiovascular disease (CVD).

A cohort study (n = 42) reported 15% versus 30% decreases in HDL-cholesterol from baseline with DMPA versus NET-EN at 1 year.[295] [EL = 2–] Another cohort study (n = 50) reported significantly lower total cholesterol concentrations in Norplant versus DMPA users after 6 months use, with no significant difference between groups in mean HDL-cholesterol, LDL-cholesterol or triglyceride concentrations.[296] [EL = 2–]

One RCT (n = 3172) reported mean reductions of 3 and 2.5 mmHg in systolic and 1.6 and 1.8 mmHg in diastolic blood pressure in DMPA and NET-EN users, respectively, at 2 years.[268] [EL = 1+]

A cohort study in Thailand comparing long-term DMPA users (n = 50) with TCu 380A IUD users (n = 50) reported no significant differences in systolic and diastolic blood pressures between the two groups at 120 months.[172] [EL = 2+]

One case–control study compared women who had used DMPA (n = 16) or COC (n = 18) for between 18 and 40 months with matched controls using no contraception (n = 18). The mean concentrations of fasting plasma total cholesterol, LDL-cholesterol and apolipoproteins were significantly higher in contraceptive users than in controls, and in COC versus DMPA users.[297] [EL = 2–]

Unlike the COC, DMPA is not associated with any increase in the risk of stroke, VTE or myocardial infarction (MI). An international hospital-based case–control study (n = 3697 cases, 1% being POIC users; n = 9997 controls) assessed CVD risks among users of progestogen-only or combined hormonal contraceptives compared with non-users of steroid hormone contraceptives. Current use of POICs did not affect combined CVD risk, or risk of stroke, VTE or acute MI. The adjusted OR for combined CVD risk in POIC users versus non-users was 1.02 (95% CI 0.68 to 1.54), for stroke 0.89 (95% CI 0.53 to 1.49), for VTE 2.19 (95% CI 0.66 to 7.26) and for acute MI 0.66 (95% CI 0.07 to 6.00).[112] [EL = 2–]

In the current WHO-MEC recommendations, DMPA and NET-EN are assigned to category '3' for women with multiple risk factors for arterial CVD, current VTE, ischaemic heart disease or history of stroke. The risks of using POICs may outweigh the benefits.[63]

DMPA is assigned to category '4' for women with a blood pressure of over 160/110 mmHg.[63]

RECOMMENDATION

Healthcare professionals should be aware that DMPA is medically safe for women to use if oestrogen is contraindicated. **D(GPP)**

Bone mineral density

Concern has been raised about the potential effects of POICs on bone mineral density (BMD) and therefore on fracture risk, particularly among young women who have not yet attained their peak bone mass and among older women, who may be starting to lose bone mass.

Several cross-sectional and cohort studies which evaluated the effects of DMPA on BMD were included in a systematic review conducted for the WHO-MEC.[298] [EL = 2++] Of these studies, few have specifically evaluated the effects of DMPA on BMD in adolescents (two cohort studies and one cross-sectional survey) or in postmenopausal women (one cross-sectional survey). No studies evaluating fracture risk in current or past DMPA users were found, nor studies evaluating BMD or fracture risk in NET-EN users.

The studies identified are heterogeneous, varying in the age group of women evaluated, in the population and settings, duration of DMPA use, site of BMD measurement, and the method used to measure BMD (three cross-sectional studies used single rather than dual X-ray absorptiometry).[299–301] Some studies compared BMD in DMPA users with users of other methods, including COCs, IUDs and Norplant. The results are inconsistent, with some studies reporting significantly lower BMD in DMPA users than non-users or users of other contraceptive methods, and others reporting no significant differences.

The results from eight cross-sectional studies[299,301–307] that measured BMD in current DMPA users (age range 17–54 years) were used to derive Z scores in a review.[308] [EL = 3] Across these studies, duration of DMPA use ranged from 1 month to at least 5 years, and the number of women evaluated ranged from 100 to 2474. The studies generally reported lower BMD in DMPA users compared with non-users, but all decreases were within 1 standard deviation of the mean of non-users (within a Z score of 1, which does not indicate osteopenia or osteoporosis). The reduction in BMD at sites of predominantly trabecular bone (lumbar spine,[302–304,306,307] femoral neck[303,304,306,307] and ultradistal radius[299,301,305]) was greater than at sites of predominantly cortical bone (midshaft ulna).[299,301,305] [EL = 3]

A 3 year US cohort study of women aged 18–39 years reported significant decreases in lumbar spine and proximal femur BMD in DMPA users (n = 182) (median duration of use of 11 months) compared with non-users (n = 258). About 34% of the latter were taking oral contraceptives, which might increase BMD. In DMPA users who discontinued the contraceptive, BMD increased at both sites.[307,309] [EL = 2+]

A Swiss cohort study (n = 45) of women aged 30–45 years reported a significant reduction in cortical bone mass at the radius in DMPA users versus users of nonhormonal contraceptives, but no significant difference between groups in changes to trabecular bone mass at 1 year.[310] [EL = 2+]

A US cross-sectional study in adolescents aged 14–18 years (n = 174) found no significant differences in BMD of the total body, hip or lumbar spine between DMPA users (median duration of use 9 months) and non-users.[311] [EL = 3]

A cohort study assessed BMD changes in adolescents (aged 14–18 years) using and discontinuing use of DMPA. It reported a significant decline in BMD at the hip and spine among DMPA users (n = 80) compared with non-users (n = 90). There was no significant difference in BMD changes for the whole body between the two groups. Of the adolescent DMPA users, 61 (71%) discontinued at some point during the 3 year follow-up, and 21% discontinued within the first 6 months of enrolment. Discontinuers experienced significantly increased BMD relative to non-users at all anatomical sites. This post-discontinuation gain in BMD suggested that the loss of bone mass may be reversible.[312] [EL = 2]

In additional to the above studies, a cross-sectional study of adolescents (n = 174) aged 14–18 years reported no significant differences in BMD of the total body, hip or lumbar spine between DMPA users (median duration of use 9 months) and non-users.[311] [EL = 3]

A cohort study of adolescents aged 11–21 years reported a significant decrease in BMD in DMPA users (n = 58) versus COC users (n = 71) at 12 and 18 (but not at 6 and 24) months.[313] [EL = 2–] One cohort study (n = 370) assessed the relationship between biochemical markers of bone metabolism and DMPA use, COC use or non-users among adolescent girls aged 12–18 years. It reported evidence of increased bone formation and resorption in those who used no hormonal contraception when compared with those in the DMPA and COC group at 12 months, suggesting possible suppression of bone metabolism in the DMPA and COC groups.[314] [EL = 2–]

A cohort study (n = 496) assessed BMD in DMPA users aged 40–49 years and reported no significant differences in BMD between users of DMPA, NET-EN, COC and non-user controls. Long-term use of DMPA does not negatively impact on BMD in women aged 40–49 years, suggesting that women can continue using this method till menopause.[315] [EL = 2+]

A cohort study in New Zealand compared the rate of menopausal bone loss in long-term users of DMPA until reaching the menopause (n = 16) with a control group of women who had not previously used DMPA and reached a natural menopause (n = 15). It reported rapid menopausal bone loss from the lumbar spine and femoral neck in the control group (6% from both sites over 3 years), and DMPA users showed little change in BMD.[316] [EL = 2–]

Among postmenopausal women who were past users of DMPA (n = 34) compared with non-users (n = 312), no significant differences in BMD of the total body, lumbar spine or femur were reported in one survey. The median duration of past DMPA use was 3 years (range 0.2 to 18.1).[317] [EL = 3]

Four cross-sectional studies reported BMD results in women who had used DMPA or a COC for at least 2 years.[299,300,318,319] Whilst one study reported that BMD at the distal radius was significantly lower in DMPA versus COC users (n = 2474),[299] the other three studies did not report significant differences in BMD at the forearm, lumbar spine or femur (n = 60, 155, 189).[300,318,319] [EL = 3] Three cohort studies also reported BMD in DMPA versus COC users, two of which were conducted in adolescents (age range 12–21 years). One of the adolescent studies reported significantly lower BMD in DMPA users versus COC users at 12 and 18 (but not 6 and 24) months.[313] [EL = 2–] The other reported that BMD decreased in users of DMPA compared with increases in COC or Norplant users, although absolute BMD values were not significantly different among groups at 1 year.[320] [EL = 2–] A US cohort study (n = 346) in new users of hormonal contraception (aged 18–33 years) reported significantly greater loss of lumbar spine

BMD in DMPA users compared with users of COCs or nonhormonal methods at 12 months.[321] [EL = 2+] In a follow-up study, the effect of DMPA use on BMD at 24 months was reported to be linear, with a total mean BMD loss of 5.7% (3.2% loss between months 12 and 24) in DMPA users versus 2.6% among pill users.[322] [EL = 2+] Another cohort study (n = 323) reported a similar linear pattern in BMD loss among DMPA users (2.8% at 12 months, accumulating to 5.7% at 24 months). Among DMPA users, BMI change was inversely associated with BMD change at the hip, but not the spine.[323] [EL = 2+]

A 6 month cohort study (n = 19) comparing BMD of the forearm and biochemical and urinary markers of bone metabolism in DMPA and Norplant users did not identify significant differences between groups in any of these parameters.[324] [EL = 2–]

A cross-sectional survey in women who had used DMPA or an IUD for at least 3 years (n = 100) reported no differences between groups in forearm BMD.[305] [EL = 3]

A small UK general practice cross-sectional study measured lumbar spine and femoral neck BMD scores in DMPA users with low oestrogen levels or displaying menopausal symptoms (n = 32). T and Z scores were below the mean at both sites. The mean duration of DMPA use was 52 months.[325] [EL = 3]

SUMMARY OF EVIDENCE

- There is conflicting evidence that DMPA reduces bone mineral density which may be reversible on discontinuation.

The Department of Health issued an alert in November 2004 on the use of DMPA,[326] advising that DMPA should be used as a first-line contraceptive in adolescents only after other methods have been discussed with the individual and considered to be unsuitable or unacceptable. Women of all ages should have the method re-evaluated after 2 years' continuous use. Women with risk factors for osteoporosis should consider other methods.

The FFPRHC also issued guidance on the use of DMPA in relation to BMD.[327]

RECOMMENDATIONS

Women should be informed that DMPA use is associated with a small loss of bone mineral density, which is largely recovered when DMPA is discontinued. **B**

Women should be informed that there is no evidence that DMPA use increases the risk of fracture. **B**

Women who wish to continue DMPA use beyond 2 years should have their individual clinical situations reviewed, the balance between the benefits and potential risks discussed, and be supported in their choice of whether or not to continue.* **D(GPP)**

Because of the possible effect on bone mineral density, care should be taken in recommending DMPA to adolescents, but it may be given if other methods are not suitable or acceptable.* **D(GPP)**

Because of the possible effect on bone mineral density, care should be taken in recommending DMPA to women older than 40 years, but in general the benefits outweigh the risks, and it may be given if other methods are not suitable or acceptable.* **D(GPP)**

Osteoporosis

We did not identify any studies assessing the effect of POIC use on osteoporosis.

RESEARCH RECOMMENDATION

Research is needed on the recovery of bone mineral density in women in the UK who have used DMPA for longer than 2 years, and the risk of fractures in older woman.

* Refer to CSM advice issued in November 2004. Go to www.mhra.gov.uk and search for Depo Provera.

Ectopic pregnancy

We did not identify any studies assessing the risk of ectopic pregnancy in women using DMPA.

Women who become pregnant while using DMPA

The WHO-MEC states that if a woman using a POIC is found to be pregnant, there is no known harm to the woman, the course of her pregnancy or the fetus. However, the relationship between DMPA use during pregnancy and its effects on the fetus remains unclear.[63] [EL = 4]

RECOMMENDATION

Healthcare professionals should be aware that if pregnancy occurs during DMPA use there is no evidence of congenital malformation to the fetus. **D(GPP)**

6.7 Return to fertility

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

Seven non-comparative studies reported that ovulation occurred between 3 to 6 months after DMPA injection.[328–333] [EL = 3]

One cohort study (n = 24) reported significant differences in the time it took for ovulation to return among DMPA and NET-EN users 90 days after their last injection (5.5 versus 2.6 months).[334] [EL = 2–]

A cohort study reported a median delay before conception of 5.5 months in DMPA users (n = 796) versus 4.5 months in IUD users (n = 125) after removal. Cumulative conception rates in the two groups were not significantly different (78% and 92% of DMPA users versus 79% and 93% of IUD users at 1 and 2 years, respectively).[335] [EL = 2–]

A cohort study (n = 98) reported no significant differences in cumulative pregnancy rates following discontinuation of Norplant or DMPA (76% versus 70%; RR 1.09, 95% CI 0.86 to 1.39 at 1 year and 90% versus 89%; RR 1.01, 95% CI 0.88 to 1.15 at 2 years).[336] [EL = 2+]

A questionnaire survey of pregnant women in the UK reported mean times to pregnancy (TTP) of 2.0, 2.2 and 3.9 times longer after the discontinuation of COC (n = 925), IUDs (n = 82) and injectables (n = 62), respectively, when compared with condom use (n = 389). Conception rates within 6 months of discontinuation were 71%, 77%, 27% and 25% among users of COC, IUDs, injectables and implants (n = 4), respectively, compared with 82% among condom users. Relative to condoms, the odds of subfecundity were 1.9, 5.5 and 2.9 among users of COC, injectables and short-term IUD, respectively. The effect of injectables was stronger with long-term use in older, obese or oligomenorrhoeic women.[209] [EL = 3]

RECOMMENDATIONS

Women should be informed that there could be a delay of up to 1 year in the return of fertility after stopping the use of injectable contraceptives. **C**

Women who stop using injectable contraceptives but do not wish to conceive should be informed that they should start using a different contraceptive method immediately even if amenorrhoea persists. **D(GPP)**

6.8 Details of method use

Assessment prior to initiation

(See Section 3.6 for recommendations.)

The UKSPR recommends that blood pressure screening is desirable before initiation of POICs.[79] [EL = 1–4]

Site of injection

Both DMPA and NET-EN injections are given by the deep intramuscular route, preferably into the gluteal region. They may be given into the deltoid in obese women where it is thought that the needle will not reach muscle.

RECOMMENDATION

Injectable contraceptives should be given by deep intramuscular injection into the gluteal or deltoid muscle or the lateral thigh. **D(GPP)**

Information prior to injection

(See Section 3.5.)

RECOMMENDATION

Women should be informed about failure rates, benefits, risks and side effects of injectable contraceptives. **D(GPP)**

Time of first injection

In a normal menstrual cycle

The UKSPR (adapted from the WHOSPR and based on evidence and consensus) recommends that progestogen-only injectables can be started up to and including the fifth day of the menstrual cycle. No additional contraceptive protection is needed. The injection can be given at any other time in the cycle if it is reasonably certain that the woman is not pregnant. Either the woman will need to abstain from sex or additional contraceptive protection should be used for the first 7 days after injection.[79] [EL = 4]

One non-comparative study (n = 150) examined the level of pregnancy risk and the bridge preferences of women requesting DMPA who were ineligible for initial injection due to the menstrual cycle day. It reported that 98% of the women rejected the standard protocol of waiting with condoms or abstinence in favour of a hormonal bridge method (oral contraceptives with the directly observed ingestion of the first pill in the clinic, or a monthly combination injection of DMPA 25 mg and estradiol cyprionate 5 mg immediately) and return to the clinic at a scheduled time to initiate DMPA. Eighty-six percent were satisfied with the bridge method. Women reporting unprotected intercourse within 120 hours before their visit received emergency contraception administered in the clinic. There were no post-treatment pregnancies.[337] [EL = 3]

Management of delayed injections

(See also Section 6.7.)

For delayed injections, the UKSPR recommends that repeat injections may be given up to 2 weeks late without additional contraceptive protection.[79] [EL = 4] If given beyond this time, additional protection is required for 7 days.

The UK Electronic Medicines Compendium (*e*MC) recommends that if the interval from the preceding DMPA injection is greater than 89 days (12 weeks and 5 days) for any reason, women should be advised to use additional contraceptive measures for 14 days after this subsequent injection.[338]

RECOMMENDATION

Women attending up to 2 weeks late for repeat injection of DMPA may be given the injection without the need for additional contraceptives.* **D(GPP)**

* At the time of publication (October 2005), this use was outside the UK marketing authorisation. 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.

Following abortion

We did not identify any studies reporting on the use of DMPA following induced abortion.

One cohort study (n = 10) reported on ovulation in women given NET-EN or an IUD on the day of first-trimester abortion. No ovulations occurred within 8 weeks of NET-EN administration. Ovulation occurred in each of the IUD users after day 25.[339] [EL = 2–]

A systematic review to update the WHO-MEC has extrapolated evidence from studies conducted with other progestogen-only methods to provide a rationale for the use of POICs post-abortion. There is no known clinical thrombogenic effect of progestogen-only contraceptives; therefore POICs can be safely used immediately following miscarriage.[264] [EL = 4]

DMPA and NET-EN are assigned to category '1' for women immediately after abortion in the current WHO-MEC recommendations.[63] [EL = 1–4]

The RCOG guideline on abortion recommends that any chosen method of contraception may be initiated immediately after abortion.[215] [EL = 1–4]

Post delivery

The UKSPR recommends that the first injection of DMPA can be given at any time between 6 weeks and 6 month postpartum if the woman is amenorrhoeic.[79] [EL = 1–4]

RECOMMENDATION

D(GPP)

Healthcare professionals should be aware that, provided that it is reasonably certain that the woman is not pregnant, the use of injectable contraceptives may be started:

- up to and including the fifth day of the menstrual cycle without the need for additional contraceptive protection
- at any other time in the menstrual cycle, but additional barrier contraception should be used for the first 7 days after the injection
- immediately after first- or second-trimester abortion, or at any time thereafter
- at any time postpartum.

6.9 Training of healthcare professionals

(See Section 3.14.)

6.10 Specific groups

Adolescents

(See Section 6.6 – Bone mineral density for recommendation.)

Women over 40 years of age

(See Section 6.6 – Bone mineral density.)

The use of POICs by women older than 40 years needs caution.[340] [EL = 2–] It is important to evaluate irregular bleeding before administering POICs, and to consider endometrial abnormalities as a possible cause if the woman returns with irregular bleeding after prolonged amenorrhoea. The inevitable loss of BMD following the menopause may be exacerbated if POICs are used during the perimenopause.

POICs are assigned to category '2' for women over 45 years of age in the current WHO-MEC recommendations.[63]

Women with body mass index over 30 kg/m²

We did not identify any studies which assessed the relationship between body weight and efficacy of POICs.

A systematic review to update the WHO-MEC reported no significant differences in the incidence of increased or excessive bleeding between obese (BMI over 30 kg/m²), overweight (BMI 25–29.9 kg/m²) and non-obese (BMI under 25 kg/m²) DMPA users of at least 9 months.[63,288] [EL = 2++]

Women who are breastfeeding

Concern has been expressed that progestogens may affect breast milk constituents and hence the baby.

A cohort study in women recruited 6 weeks after childbirth (n = 140) reported that mean milk concentrations of calcium, phosphorus, sodium, potassium and protein were similar at 26 weeks postpartum in users of POICs (oral or DMPA, n = 51) and nonhormonal contraception (n = 89). Triglyceride levels were significantly higher in the women using progestogen-only methods, and magnesium levels were significantly higher in the women using nonhormonal methods.[341] [EL = 2–]

Two US cohort studies investigated the impact of DMPA on breastfeeding in postpartum women. One (n = 319) reported no significant differences between groups in the proportion of women who continued to breastfeed, supplemented breastfeeding with bottle-feeding, or who discontinued breastfeeding within 6 weeks postpartum due to insufficient milk.[342] [EL = 2+] Another cohort study (n = 95) reported no differences between users of DMPA or nonhormonal contraception in the duration of breastfeeding or in the timing of the first introduction of formula feed during the first 16 weeks postpartum.[343] [EL = 2+]

DMPA and NET-EN are assigned to category '3' for women during the first 6 weeks postpartum and who are breastfeeding in the current WHO-MEC recommendations.[63] [EL = 1–4] The UKSPR states that for women who are less than 6 weeks postpartum and primarily breastfeeding, POICs are not usually recommended unless other methods are not available or are unacceptable.[79]

DMPA and NET-EN are assigned to category '1' for women who are 6 weeks or over 6 weeks postpartum and breastfeeding in the current WHO-MEC recommendations.[63] [EL = 1–4]

RECOMMENDATIONS

Healthcare professionals should be aware that women with a body mass index over 30 can safely use DMPA and NET-EN. **D(GPP)**

Healthcare professionals should be aware that women who are breastfeeding can consider using injectable contraceptives. **C**

6.11 Medical conditions and contraindications

Diabetes

We did not identify any studies which addressed the effect of POIC use in women with diabetes.

Epilepsy

In a case-series study, MPA (oral in 8 women, DMPA in 6 women) was added to the anti-epileptic drug regimen of those who had uncontrolled seizures. Significant reductions (39%) in mean monthly seizure frequency were reported from baseline.[344] [EL = 3]

DMPA and NET-EN are assigned to category '1' for women with epilepsy in the current WHO-MEC recommendations.[63] [EL = 1–4]

Sexually transmitted infections, HIV and AIDS

(See Section 3.11.)

A systematic review to update the WHO-MEC reported limited evidence that there may be an increased risk of chlamydial cervicitis, a lower genital tract infection, among DMPA users at high risk of STIs. Evidence for risks of other STIs is insufficient and inconclusive.[63,219] [EL = 1–4]

The use of hormonal contraceptives by women who are HIV-1 seronegative has been associated with an increased risk of the acquisition of cervical STI, including chlamydial infection, gonorrhoea and non-specific cervicitis.[345–347]

A 10 year cohort study (n = 242) in Kenya evaluated the relationship between hormonal contraceptive use and the acquisition of STI among HIV-infected women. It reported a significant increased incidence of cervical chlamydial infection (hazard ratio 3.1; 95% CI 1.2 to 8.4) and cervicitis (hazard ratio 1.6; 95% CI 1.1 to 2.4) in DMPA users (n = 79) when compared with women who used no contraceptive method (n = 124). OC users (n = 37) had a significantly increased incidence of cervicitis (hazard ratio 2.3; 95% CI 1.4 to 3.6).[348,349] [EL = 2–]

A systematic review to update the WHO-MEC reported inconsistent evidence regarding the increased risk of HIV acquisition among users of progestogen-only contraceptives compared with non-users. There is conflicting evidence on whether there is an increased risk of HIV and herpes simplex virus (HSV) shedding among HIV-infected women using DMPA.[63,219] [EL = 1–4]

RECOMMENDATION

Healthcare professionals should be aware that: **D(GPP)**

- injectable contraceptives are not contraindicated in women with diabetes
- DMPA use may be associated with a reduction in the frequency of seizures in women with epilepsy
- there is no evidence that DMPA use increases the risk of STI or HIV acquisition
- DMPA is a safe and effective method of contraception for women with STIs, including HIV/AIDS (safer sex using condoms should be encouraged in this group).

6.12 Drug interactions

The UK Summary of Product Characteristics (SPC) for DMPA states that 'the clearance of medroxyprogesterone acetate is approximately equal to the rate of hepatic blood flow. Because of this fact it is unlikely that drugs which induce hepatic enzymes will significantly affect the kinetics of medroxyprogesterone acetate. Therefore no dosage adjustment is recommended in patients receiving drugs known to affect hepatic metabolising enzymes.'

The SPC for NET-EN states that 'Some drugs may accelerate the metabolism of Noristerat. Drugs suspected of having this capacity, which may reduce the efficacy of the preparation, include barbiturates, carbamazepine, phenytoin, phenylbutazone, griseofulvin and rifampicin. The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.'

RECOMMENDATION

Healthcare professionals should be aware that women taking liver enzyme-inducing medication may use DMPA and that the dose interval does not need to be reduced. **D(GPP)**

6.13 Follow-up

We did not identify any studies which addressed follow-up care in women using DMPA or NET-EN.

Repeat DMPA injections should be provided every 12 weeks, and repeat NET-EN injection every 8 weeks.

In a 1 year RCT (n = 250), sending reminders of their next injection to women did not reduce the number of missed appointments compared with those not sent a reminder (39% versus 33%; RR 1.16, 95% CI 0.83 to 1.62). Continuation rates were not significantly different between groups (43% versus 45%; RR 0.94, 95% CI 0.71 to 1.25).[350] [EL = 1+]

7. Progestogen-only subdermal implants (POSDIs)

7.1 Introduction

What they are

Contraceptive implants are inserted subdermally under the skin in the upper arm. Implanon is currently the only subdermal implant licensed for use in the UK. Norplant has not been marketed in the UK since 1999. However, it is still in use in many other countries and women still attend UK clinics requesting removal. Jadelle® (Norplant-2) has not been marketed in the UK, but is licensed elsewhere in the world and women sometimes attend UK clinics requesting removal.

Mechanism of action

Implanon is a single-rod contraceptive implant (40 mm × 2 mm) which contains 68 mg of etonogestrel (ENG) dispersed in a membrane of ethylene vinyl acetate. Implanon delivers ENG at a dose sufficient to suppress ovulation in every cycle throughout the 3 years of use.[351,352]

Norplant consists of six flexible, sealed capsules (34 mm × 2.4 mm), each containing 36 mg of levonorgestrel (LNG). Norplant-2 (Jadelle) consists of two rods containing a total of 150 mg of LNG. Norplant and Jadelle prevent normal sperm transport by altering the characteristics of cervical mucus and also by preventing normal development of the endometrium.[351] The dose of LNG delivered with time falls significantly. In the first year of use fewer than 10% of cycles are ovulatory. By the fifth year ovulation occurs in more than 50% of cycles.[353,354]

RECOMMENDATION

Women should be informed that Implanon acts by preventing ovulation. **C**

Use in Great Britain

In 2003/04, it was estimated that fewer than 3% of women aged 16–49 years in Great Britain use the implants as their method of contraception.[1] [EL = 3].

Duration of action

Implanon is licensed for 3 years. Norplant and Jadelle are both licensed for 5 years.

RECOMMENDATION

Women should be informed that Implanon has UK Marketing Authorisation for use for 3 years **D**

The evidence

A systematic review designed to assess relative effectiveness, acceptability, tolerability and cost effectiveness of Norplant, Jadelle and Implanon was undertaken by the NHS Health Technology

Assessment (HTA) Programme in the late 1990s.[126] For subdermal contraceptive implants, 34 comparative studies met the inclusion criteria for the review, including 15 RCTs and 19 non-randomised prospective cohort studies.

The majority of the studies (59%) were undertaken in developing countries and 12% were multicentre studies which included sites in developing countries. The RCTs included a total of 1771 women from developing countries and 656 women from developed countries. The cohort studies recruited 5045 women from developing countries and 459 women from developed countries.

The GDG has reservations about the relevance of many of these studies to the UK population. For example, the group felt it inappropriate to use data on continuation rates from countries where access to contraception is limited and/or expensive. Similarly, data from countries where women are characteristically of significant lower body weight (such as Indonesia or Thailand) than women in the UK may overestimate the effectiveness of hormonal methods of contraception and the incidence of amenorrhoea. (See Sections 3.4 and 3.10.) Additionally, some of the studies used to compare the effectiveness of implants with other methods included in the HTA review were limited to specific subgroups, such as adolescents or breastfeeding women. The GDG did not feel it appropriate to use data from these studies in considering women of reproductive age in the general population in the UK.

Available data on the effectiveness and efficacy of Implanon are currently limited to a number of clinical trials conducted by the manufacturer comparing Implanon and Norplant in multicentre studies in the period 1989 to 1998 (2423 women, 75 050 cycles in the Implanon group versus 819 women, 28 109 cycles in the Norplant group). Data from these clinical trials (a total of 8 RCTs and 12 non-comparative studies) formed one integrated database and have been analysed by one systematic review[126] and a series of meta-analyses.[355–360] Reports from individual trials from the same series have also been published by various authors.[53,361–365]

We received information in July 2004 from the relevant pharmaceutical company that, as a result of protocol violation, data from five trials (three RCTs and two non-comparative studies) carried out in Indonesia were to be excluded retrospectively. A revised analysis, including data from new trials, was expected in November 2004. However, no revised analysis was available and evidence from one non-comparative study[53] to represent the clinical efficacy of Implanon was resubmitted.

A press report issued by the Dutch Medicines Evaluation Board at The Hague in October 2004 stated that Implanon is 'still considered to be effective and safe, provided it is inserted in the appropriate manner according to the product information.[366] Evidence which compares Implanon with Norplant presented in this chapter is based on original published data from these clinical trials and may contain data from Indonesia before the Indonesian trials were withdrawn, and should therefore be interpreted accordingly. References to these trials are marked with an asterisk (*).

Where no studies comparing the use of Implanon with other methods of contraception were identified, indirect evidence from Norplant studies was reviewed (and extrapolation made). The GDG is aware that Implanon and Norplant differ in many respects. They contain different progestogens, the duration of action differs and the number of implants differs. Importantly, in terms of both efficacy and side effects, Implanon inhibits ovulation in almost all women for 3 years while the number of ovulatory cycles increases with time among Norplant users. By 5 years, over 50% of Norplant cycles are ovulatory. The presence or absence of ovulation significantly affects bleeding patterns and thereby side effects. In the absence of long-term data on Implanon, and where the GDG felt that it was reasonable to do so, data on Norplant has been included. Since Implanon is licensed for 3 years and Norplant for 5 years, wherever possible data from Norplant use at 3 years have been used. Data on Norplant, particularly on efficacy, come largely from trials sponsored and/or organised by the developer of the product (a not-for-profit organisation).

7.2 Effectiveness

Implanon versus Norplant

Two meta-analyses of clinical trials (8 RCTs and 12 cohort studies, n = 2043 women, 74 000 cycles) reported no pregnancies and no ectopic pregnancies in women using either Implanon or Norplant at 3 years.[355*,356*] [EL = 1–]

A NICE technology appraisal (7 RCTs, 1628 women, 43 001 woman-months of follow-up) reported no pregnancies at 4 years among women using Implanon or Norplant.[126*] [EL = 1–] The RCTs reviewed were part of the multinational clinical trials conducted by a pharmaceutical company.[355*]

A cohort study in China that compared the use of Implanon (n = 75) and Norplant (n = 25) reported no pregnancies in either group at 4 years.[367] [EL = 2–]

Implanon

A non-comparative study (n = 60) in Spain reported no pregnancies among Implanon users at 1 year.[368] [EL = 3]

A retrospective case note review (n = 132) of Implanon users in the UK reported no known pregnancies at 3 years (15% of women were lost to follow-up).[369] [EL = 3]

The GDG was aware that pregnancies have been reported during Implanon use. Spontaneous reports to the Medicines and Healthcare products Regulatory Agency (MHRA) (through the Yellow Card scheme) of suspected adverse drug reactions relating to Implanon included 115 unintended pregnancies from 1999 to 2005. (NB. This does not necessarily mean that use of Implanon caused the reaction.)[370]

MDA National, a medical indemnity insurer in Australia, quoted that about 100 pregnancies have been reported in Australia in the first 18 months of use of Implanon (unpublished data from Organon Australia submitted to MDA National, www.mdanational.com.au).[371]

During the first 3 years of marketing in Australia, 218 unintended pregnancies associated with Implanon were reported to the Australian Adverse Drug Reactions Advisory Committee. The reasons for unintended pregnancy were non-insertion (84), incorrect timing (19), drug interaction (8), Implanon expelled (3), product/method failure (13), prior conception (46) and insufficient information (45).[372] [EL = 3]

SUMMARY OF EVIDENCE

- No pregnancies were reported in clinical studies in women using Implanon.
- From the clinical experience of the GDG and from post-marketing surveillance, there were reports of pregnancies using Implanon.

RECOMMENDATION

Women should be informed that the pregnancy rate associated with the use of Implanon is very low (fewer than 1 in 1000 over 3 years). **C**

7.3 Discontinuation and reasons for discontinuation

(See Section 3.10.)

Most methods of contraception can be discontinued without the involvement of a healthcare professional. However, to stop using an implant a woman does need to visit a health service facility. In the UK, a relatively small number of healthcare professionals have been trained to remove implants. The geographical inconvenience of attending a particular clinic for implant removal may mean women have to postpone removal for longer.[373] In many countries the cost to the individual of the implant and implant insertion and the additional cost of both removal of

the implant(s) and provision of a new method may encourage longer continuation than that typical of the UK. Evidence on continuation rates for Norplant beyond 3 years of use was ignored by the GDG since Implanon is only licensed for 3 years.

Implanon versus Norplant

The overall cumulative discontinuation rate was reported to be 18% at 2–3 years. The major reasons for discontinuation were bleeding irregularities (but not amenorrhoea) and adverse effects.[356*] Cumulative discontinuation rates due to amenorrhoea and bleeding irregularities between Implanon and Norplant users in the European RCTs were 30.2% versus 22.5% at 2 years. Three meta-analyses of clinical trials reported adverse events other than bleeding irregularities as the primary reason for discontinuation in 6% of Implanon users versus 7.6% of Norplant users at 2 years.[355*,356*,359*] [EL = 1– to 3]

One non-comparative study (n = 635, part of a European multicentre RCT) reported cumulative discontinuation rates of 20% and 31% at 1 and 2 years, respectively. Cumulative discontinuation rates due to bleeding irregularities were 17% and due to amenorrhoea 1.7% at 2 years.[53] [EL = 3]

Interim data from an unpublished study in Edinburgh (n = 329 Implanon insertions; data completed on 271 women) reported a removal rate of 11% within 6 months, 25% at 1 year and 55% at 2 years and 9 months. Of those requiring ongoing contraception, 47% requested a new implant. Discontinuation due to planned pregnancy was 10% and 8% discontinued because the women had no partners. The most frequent reported reason for discontinuation was bleeding (32% due to amenorrhoea or frequent bleeding episodes).[374] [EL = 3]

Implanon

A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported the premature removal of Implanon in 24% of users, primarily because of side effects (20%). Side effects leading to discontinuation were mainly bleeding disturbances (45%), acne (12%), weight gain (7%), depressive moods (5%) and insertion site problems (3%) among Implanon users at 9 months.[375] [EL = 3]

A non-comparative study (n = 60) in Spain reported a discontinuation rate of 1.7% due to bleeding disturbances at 1 year.[368] [EL = 3]

A retrospective chart review (n = 132) in the UK reported a removal rate of 17% among Implanon users at the end of the 3 year study period. The primary reasons for Implanon removal were abnormal bleeding (12%) and severe mood changes (9%). Using the Kaplan–Meier method, this study calculated that the assumed lifetime probabilities of Implanon still being in place were 0.90 (95% CI 0.82 to 0.95) at 1 year, 0.80 (95% CI 0.67 to 0.88) at 2 years and 0.75 (95% CI 0.58 to 0.85) at 36 months. The confirmed lifetimes were 0.84 (95% CI 0.71 to 0.91) at 12 months, 0.63 (95% CI 0.42 to 0.78) at 24 months and 0.53 (95% CI 0.28 to 0.73) at 36 months. Older women are less likely to have an implant removed for all side effects (hazard ratio 0.9; 95% CI 0.81 to 0.99).[369] [EL = 3]

A retrospective non-comparative study (n = 108) in France reported a removal rate of 27% at 16 months among Implanon users. The reasons for discontinuation included menorrhagia (41%), amenorrhoea (21%), weight gain (21%), acne (14%), headaches (10%) and loss of libido (3%). In this study, the average duration of Implanon use was 16 months.[376] [EL = 3]

SUMMARY OF EVIDENCE

Table 7.1 Implanon: cumulative discontinuation rates

Study	Cumulative discontinuation rate (%)	Rate measured at point (month)	EL
356	18	24	3
53	20 31	12 24	3
374	25 44 55	12 24 33	3
375	24	9	3
369	17	36	3
376	27	16	3

- The most common reason for discontinuation of contraceptive implants is bleeding disturbances.
- Almost one-third of women will have had an implant removed within 2 years because of bleeding problems.
- Six percent of women will discontinue Implanon within 2 years for reasons other than bleeding disturbance, including reasons attributable to hormonal changes.

RECOMMENDATION

Healthcare professionals should be aware that:

- up to 43% of women stop using Implanon within 3 years
- 33% of women stop because of irregular bleeding
- less than 10% of women stop for other reasons including hormonal (non-bleeding) problems.

C

7.4 Adverse effects

A systematic review to update the WHO-MEC recommendations reported no serious adverse effects among healthy Implanon users.[377] [EL = 1–3] Implanon and Norplant are assigned a category '1' rating for healthy women from menarche to before the menopause (18 to > 4 years).[63] [EL = 1–4]

A meta-analysis of clinical trials reported no deaths in any of the clinical development trials of Implanon.[355*] [EL = 3] A 5 year multicentre controlled cohort study (n = 16 021 women), undertaken mainly in developing countries, comparing the effectiveness and safety of Norplant, IUDs, COC and sterilisation reported 34 deaths, of which 11 were in Norplant users. Five deaths were related to accidents, two suicides, one as a result of lymphoma and one from stroke. The remaining two deaths were related to the reproductive system: one as a result of septic abortion 1 year after Norplant removal; the other death occurred in a woman with a clinical diagnosis of metastatic breast cancer.[114,176] [EL = 2+] None of these deaths was considered to be a direct consequence of the contraceptive implant.

Implanon

A retrospective non-comparative study (n = 108) in France reported that, of the 81% of women who were satisfied with the use of Implanon, adverse effects occurred in 47% of the women in this group at 20 months.[376] [EL = 3]

SUMMARY OF EVIDENCE

- In the absence of long-term data on Implanon, the GDG considered it appropriate to extrapolate from Norplant data.
- Implanon use is not associated with serious adverse effects.

Bleeding problems

Bleeding patterns experienced by women using progestogen-only contraceptive methods include regular bleeding episodes, amenorrhoea, dysmenorrhoea, infrequent bleeding, frequent bleeding, and prolonged and heavy bleeding.

Disturbances of menstrual bleeding are common among women who are not using contraception. The prevalence of dysmenorrhoea in the general population is estimated to be about 72% in young women.[378] In untreated women, amenorrhoea occurs in about 1% of women aged 30 years. The figures for infrequent bleeding and prolonged bleeding are about 8% and < 0.1%, respectively.[379]

Implanon versus Norplant

One meta-analysis of clinical trials reported significant differences in the occurrence of amenorrhoea (21.1% in Implanon users versus 4.7% in Norplant users) and infrequent bleeding (27.3 % versus 21.1%), but no differences in frequent bleeding (6.1% versus 3.4%) or in prolonged bleeding (12.1% versus 9.0%) at 2 years.[355*] [EL = 1–] About 40% of the women experienced mild or severe dysmenorrhoea at entry to the study. The incidence of dysmenorrhoea changed from 59% and 51% at baseline to 9% and 21% at removal in the Implanon and Norplant groups, respectively.[356*,359*] [EL = 1–]

(See Section 7.3.)

Implanon

A retrospective case note review (n = 132) in the UK reported a cumulative removal rate of 12% among Implanon users due to bleeding problems as the primary reason at 3 years. Bleeding disturbances were reported by 26% of Implanon users. They included prolonged bleeding (31%), oligomenorrhoea/amenorrhoea (27%) and irregular bleeding (13%). Normal cycles were reported in 28% of Implanon users at 3 years.[369] [EL = 3]

A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported a discontinuation rate due to bleeding disturbances of 45%. Side effects related to bleeding included infrequent bleeding (28%), amenorrhoea (33%), prolonged bleeding (15%) and metrorrhagia (16%) at 1 year.[375] [EL = 3]

A non-comparative study (n = 60) in Spain reported normal cycles (50%), infrequent bleeding (16%), frequent bleeding (3%), prolonged bleeding (5%) and amenorrhoea (12%) among Implanon users at 1 year.[368] [EL = 3]

A retrospective non-comparative study (n = 108) in France reported that menstrual disturbances occurred in 83% of Implanon users, mainly amenorrhoea (26%) and irregular bleeding (40%) at 20 months. Dysmenorrhoea was improved and disappeared in 16% and 14% of women using the implant.[376] [EL = 3]

SUMMARY OF EVIDENCE

- Many women using Implanon will experience a change in bleeding pattern: approximately 20% of users will experience amenorrhoea; approximately 45% of users will experience either infrequent, frequent, or prolonged bleeding; and dysmenorrhoea is significantly reduced.
- As levonorgestrel concentrations fall with time and ovulation becomes more likely among Norplant users, bleeding episodes tend to become more regular. Since the effect of Implanon on ovulation inhibition is consistent for all 3 years of use, bleeding patterns are unlikely to change with time.

RECOMMENDATIONS

Women should be informed that: **C**

- bleeding patterns are likely to change while using Implanon
- 20% of women will have no bleeding, while almost 50% of women will have infrequent, frequent or prolonged bleeding

- bleeding patterns are likely to remain irregular over time. C

Healthcare professionals should be aware that dysmenorrhoea may be reduced during the use of Implanon. C

Management of bleeding problems

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

Norplant and mefenamic acid

An RCT compared the non-steroidal anti-inflammatory agent mefenamic acid with placebo in Norplant users. Bleeding was stopped in a significantly higher number of women in the mefenamic acid group (n = 34) than in the placebo group (n = 33) at 1 week (76% versus 27%) and at 4 weeks (68% versus 33%). There was a significant decrease in mean number of days of bleeding in the mefenamic acid group when compared with the placebo group (11.6 ± 8.2 versus 17.2 ± 10.2 days) at 4 weeks.[380] [EL = 1+]

Norplant and ethinylestradiol

One RCT compared a levonorgestrel-containing COC versus ethinylestradiol alone versus placebo in Norplant users. The mean number of bleeding days was significantly lower in the COC group (n = 45) than in the ethinylestradiol group (n = 43) or the placebo group (n = 46) (2.6 ± 1.4 versus 5.4 ± 5.1 versus 12.3 ± 5.4 days). Bleeding stopped within 7 days in 2%, 14% and 50% of the COC, ethinylestradiol and placebo groups, respectively. The COC was more effective than ethinylestradiol alone.[381] [EL = 1+]

Preliminary results from another RCT reported a significant reduction in the mean number of bleeding days at 3 months in Norplant users treated with either ethinylestradiol (n = 18) or the combined pill (n = 16) when compared with placebo (n = 14) (19.2 ± 3.4 versus 18.2 ± 1.9 versus 28.6 ± 5.4 days).[382] [EL = 1+]

An RCT reported no significant difference in the clinical improvement of bleeding problems in Norplant users with a transdermal estradiol patch (n = 33) when compared with a placebo patch (n = 31) (70% versus 42%).[383] [EL = 1+]

Norplant and vitamin E

Preliminary results from an RCT reported a significant reduction in the mean number of bleeding days in Norplant users treated with vitamin E supplementation (n = 38) when compared with a placebo (n = 34) (7.7 ± 1.4 days versus 12.1 ± 1.3 days).[384] [EL = 1+]

A multicentre RCT compared vitamin E (n = 120), aspirin (n = 122), vitamin E and aspirin (n = 121) and placebo (n = 123) in the treatment of Norplant-induced prolonged vaginal bleeding. No significant reduction occurred in the length and duration of bleeding/spotting episodes or bleeding-free intervals with any of these treatments in Norplant users.[385] [EL = 1–]

Norplant and the antiprogesterone mifepristone

One RCT compared mifepristone and placebo in the treatment of bleeding disturbances among Norplant users during the first year of use. It reported that all women, regardless of treatment, experienced significantly reduced frequency of bleeding over the 1 year of observation. Women who received mifepristone treatment (n = 50) reported significantly shorter episodes of bleeding when compared with the placebo group (n = 50) (48 ± 15 days versus 51 ± 15 days) during the first 90 days. There was a significant reduction in the mean duration of bleeding episodes between the two groups (14 days before mifepristone treatment down to 6.5 days versus 15 days down to 11.1 days).[386] [EL = 1+]

Another RCT reported the same frequency of bleeding/spotting episodes but significantly fewer prolonged bleeding episodes in Norplant users receiving mifepristone (n = 58) when compared with the placebo group (n = 57) (11 ± 3 days versus 22 ± 23 days). The total number of bleeding days was 35% lower than in the placebo group.[387] [EL = 1+]

SUMMARY OF EVIDENCE

- There is some evidence to support a beneficial effect of mefenamic acid, ethinylestradiol (alone or as an OC) or mifepristone on bleeding patterns in Norplant users. It is biologically plausible that the same will be true for Implanon.
- There is no evidence to support the use of Vitamin E or aspirin, and insufficient evidence for NSAID use in managing abnormal bleeding.
- There are no data on long-term treatment.

RECOMMENDATION

Healthcare professionals should be aware that irregular bleeding associated with implant use can be treated with mefenamic acid or ethinylestradiol.* **B**

7.5 Common concerns and symptoms

Weight change

Weight fluctuation in women of reproductive age is common. Many women are concerned that hormonal contraceptive use may lead to weight gain.

Implanon versus Norplant

A meta-analysis reported weight increase (of > 10% from baseline at least once during implant use) in 8.7% of Implanon and Norplant users at 4 years.[355*] [EL = 1–]

Implanon

A retrospective case note review (n = 132) in the UK reported that weight gain was experienced in 4% in Implanon users at 3 years. No objective measurement of body weight was made.[369] [EL = 3]

A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported weight gain in 9% of Implanon users at follow-up (n = 306, mean duration 11.4 months).[375] [EL = 3]

A non-comparative study (n = 60) in Spain reported significant changes in mean weight from baseline (65.1 kg to 59.7 kg) among Implanon users at 4 months, but at 6 months, mean weight reached values similar to baseline (58.9 kg). Weight increase was reported by 5% of women in this study.[368] [EL = 3]

A retrospective non-comparative study (n = 108) in France reported no change in weight, weight gain and weight loss in 52%, 37% and 11%, respectively, of Implanon users at follow-up (mean duration 16 months).[376] [EL = 3]

SUMMARY OF EVIDENCE

- There is no evidence to support a causal association between the use of Implanon and weight change.

Altered mood

Implanon

A retrospective case note review (n = 132) in the UK reported mood changes in 11% of Implanon users at 3 years. As the primary reason, severe mood changes accounted for 9% of all Implanon removals.[369] [EL = 3]

* The recommendation on treating irregular bleeding after insertion of a contraceptive implant has been changed (this is recommendation 1.5.4.2 in the NICE guideline). Although the evidence does show that mifepristone is effective at controlling irregular bleeding associated with implants, it is not licensed for this indication. The revised recommendation reads: 'Irregular bleeding associated with implant use can be treated with mefenamic acid or ethinylestradiol.'

A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported mood swings and depressive mood in 3% and 2%, respectively, of Implanon users at follow-up (n = 306, mean duration 11.4 months).[375] [EL = 3]

A non-comparative study (n = 60) in Spain reported nervousness in 2% of Implanon users at 1 year.[368] [EL = 3]

A retrospective non-comparative study (n = 108) in France reported the occurrence of sad mood in 10% of Implanon users at follow-up (mean duration 16 months).[376] [EL = 3]

SUMMARY OF EVIDENCE

- Non-comparative studies reported that fewer than 10% of women give mood change as the reason for discontinuing Implanon.

Altered libido

The experience of sexual dysfunction, such as loss of libido, is common among young women, and the incidence ranges from 5% to 30%.[169,170]

A meta-analysis of clinical trials reported incidences of emotional lability and decreased libido of 4.9% and 3.3%, respectively, in Implanon users versus 7.6% and 5.4%, respectively, in Norplant users.[355*] [EL = 1–]

Implanon

A retrospective case note review (n = 132) in the UK reported loss of libido in 1% of Implanon users at 3 years.[369] [EL = 3]

A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported loss of libido in 1% of Implanon users at follow-up (n = 306, mean duration 11.4 months).[375] [EL = 3]

A non-comparative study (n = 60) in Spain reported loss of libido in 2% of Implanon users at 1 year.[368] [EL = 3]

A retrospective non-comparative study (n = 108) in France reported that low libido did not occur among Implanon users at follow-up (mean duration 16 months).[376] [EL = 3]

SUMMARY OF EVIDENCE

- Non-comparative studies reported that fewer than 2% of women complain of loss of libido during use of Implanon.

Acne

Acne is a common skin condition affecting 35% to 90% of adolescents.[293] Progestogens, particularly the more androgenic ones such as LNG, are a potent stimulus to sebum secretion which tends to make the skin greasier and prone to acne.[247] In contrast, the combined oral contraceptive is beneficial for acne, and thus women who change from a combined method to a progestogen-only method may notice an increase in acne.

Implanon versus Norplant

A meta-analysis of clinical trials reported an incidence of acne of 18.5% and 21.2% in Implanon and Norplant users (aged 18–40 years), respectively. No baseline data were available.[355*] [EL = 1–]

Implanon

Data from one non-comparative study (n = 635, part of a European multicentre RCT) reported that acne occurred or worsened in 12.6% of Implanon users, whereas acne improved in 12.8% of Implanon users at follow-up (mean duration 16 months).[53] [EL = 3]

A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported acne in 12% of Implanon users at follow-up (n = 306, mean duration 11.4 months).[375] [EL = 3]

A non-comparative study (n = 60) in Spain reported acne in 3% of Implanon users at 1 year.[368] [EL = 3]

Another retrospective non-comparative study (n = 108) in France reported the occurrence of acne in 9% and the worsening of acne in 4% of Implanon users at follow-up (mean duration 16 months).[376] [EL = 3]

SUMMARY OF EVIDENCE

- Non-comparative studies reported that acne may improve or develop during Implanon use.

Headache

Headache is one of the most common symptoms experienced in the general population, both in young people and in adults. About 70% of adults report headache in the previous 3 months; the prevalence is greater in females than in males.[248] The prevalence of migraine has been estimated to be about 7% among adolescents.[294]

Implanon versus Norplant
A meta-analysis of clinical trials reported incidences of headache in 16.8% and 20.1% of Implanon and Norplant users, respectively.[355*] [EL = 1–]

Implanon
A multicentre retrospective non-comparative study (n = 1183) in Switzerland reported headaches in 4% of Implanon users at follow-up (n = 306, mean duration 11.4 months).[375] [EL = 3]

A retrospective chart review (n = 132) in the UK reported headaches in 1% of Implanon users at 3 years.[369] [EL = 3]

Another retrospective non-comparative study (n = 108) in France reported the occurrence of headaches in 18% and the worsening of headaches in 3% of Implanon users at follow-up (mean duration 16 months).[376] [EL = 3]

SUMMARY OF EVIDENCE

- Non-comparative studies reported that the incidence of headache is not increased among women using Implanon.

RECOMMENDATIONS

Women should be informed that Implanon use: **C**

- is not associated with changes in weight, mood, libido or headaches
- may be associated with acne.

Healthcare professionals should be aware that all progestogen-only methods, including contraceptive implants, may be used by women who have migraine with or without aura. **D(GPP)**

7.6 Risks

Cardiovascular disease

Oestrogen-containing hormonal contraceptives are associated with an increased incidence of VTE. Concern has also been raised regarding the association of metabolic alterations caused by hormonal contraceptive with coronary artery disease

Implanon versus Norplant
One RCT (n = 86) reported similar small effects on the haemostatic system among both Implanon and Norplant users. These effects are not suggestive of an increased tendency towards thrombosis.[388] [EL = 1+]

A meta-analysis of clinical trials reported a low incidence of increased blood pressure in both Implanon and Norplant users. There was an increase of 0.1% versus 0.9% in systolic and 0.4%

versus 0.7% in diastolic blood pressure in Implanon and Norplant users, respectively.[355,358*] [EL = 1–]

The risk of cardiovascular disease and serum lipid profile may be related. One RCT (n = 60) reported that all changes in serum apolipoprotein concentrations, irrespective of an increase or decrease, were not significantly different from baseline among Implanon and Norplant users at 2 years. There was also no significant difference in serum apolipoprotein concentrations between the two groups.[389] [EL = 1–]

Another RCT (n = 90) reported small changes from baseline in circulation concentrations of lipids and apolipoproteins. There was no significant change in these parameters among either Implanon or Norplant users at 3 years.[390] [EL = 1–]

One RCT (n = 80) reported no significant changes in serum lipid ratios among either Implanon or Norplant users at 2 years.[391] [EL = 1–]

Alterations in glucose and insulin levels may be related to the risk of cardiovascular disease.[392] An RCT (n = 80) reported that both Implanon and Norplant induced mild insulin resistance. Although there was a significant increase in serum glucose levels from baseline in the two groups (values well within the WHO criteria for impaired glucose tolerance), there were no significant differences in changes in serum glucose levels between the two groups at 6, 12 and 24 months.[393] [EL = 1–]

Implanon

A non-comparative study (n = 60) in Spain reported no clinically significant changes in blood pressures, blood cholesterol or glucose concentrations among Implanon users at 1 year.[368] [EL = 3]

In the current WHO-MEC recommendations, implants are assigned to category '2' for initiation category '3' for continuation in women with current and history of arterial cardiovascular disease and hypertension and stroke.[63] [EL = 1–4]

SUMMARY OF EVIDENCE

- There is no evidence for an adverse effect of contraceptive implants on blood pressure, on the risk of VTE or on known biomedical markers for increased risk of cardiovascular disease.

Bone mineral density

There has been concern about the potential effects of progestogen-only injectable contraceptives such as DMPA on bone mineral density (BMD), particularly among young women who have not yet reached peak bone mass and among older women, who may be starting to lose bone mass.[394] There is an association between the suppressive effect of progestogen on ovarian oestrogen secretion and bone loss.[395]

Implanon versus other contraceptive methods

A cohort study (n = 73) which compared Implanon with a copper IUD reported no significant difference in changes from baseline in BMD in and between the two groups over a period of 2 years. The clinically significant mean decrease in BMD of one standard deviation was not reached at any point.[396] [EL = 2+]

Implanon

A systematic review to update the current WHO-MEC recommendations reported no evidence of an adverse effect on BMD among healthy Implanon users.[377] [EL = 1–3]

SUMMARY OF EVIDENCE

- There is no evidence for a clinically significant effect of Implanon on BMD.

RECOMMENDATION

Healthcare professionals should be aware that:

C

- contraceptive implants are medically safe for women to use if oestrogen is contraindicated
- there is no evidence of an effect of Implanon use on bone mineral density.

Ectopic pregnancy

The risk of ectopic pregnancy increases with age. It is estimated that the incidence of ectopic pregnancy ranged from 3 to 4.5 per 1000 women-years among non-contraceptors.[175] Since ovulation is inhibited throughout the 3 years of use, the risk of ectopic pregnancy among Implanon users should be much reduced compared with that for women not using contraception.

We did not identify any studies which assessed the occurrence of ectopic pregnancy in Implanon users.

A 5 year multicentre controlled cohort study (n = 16 021 women), undertaken mainly in developing countries, reported an ectopic pregnancy rate of 0.30, 0.68 and 0.13 per 1000 woman-years in users of Norplant, copper-IUDs and sterilisation, respectively.[114] [EL = 2+]

One multinational RCT comparing Jadelle (n = 598) with Norplant (n = 600) reported ectopic pregnancy rates of 0.4 versus 0 per 1000 women-years at 5 years.[397] [EL=1–]

A US non-comparative study of a variant of LNG capsule implants (n = 511) reported an ectopic pregnancy rate of 0.6 per 1000 women-years at 5 years.[60] [EL = 3]

SUMMARY OF EVIDENCE

- No studies were identified looking at ectopic pregnancy and Implanon use.
- The rate of ectopic pregnancy in other subdermal implants which do not always block ovulation is extremely low.
- On theoretical grounds, the rate for Implanon (which blocks ovulation) would be even lower.

Women who become pregnant while using implants

The WHO-MEC states that if a woman using progestogen-only implants is found to be pregnant, there is no known harm to the woman, the course of her pregnancy or the fetus.[63] [EL = 4] However, if she plans to continue the pregnancy the implant should be removed as soon as possible as virilisation of the fetus may theoretically occur.

RECOMMENDATION

Healthcare professionals should be aware that there is no evidence of a teratogenic effect of Implanon use, but, if a woman becomes pregnant and continues with the pregnancy, the implant should be removed.

D(GPP)

7.7 Return to fertility

A meta-analysis of clinical trials reported return of ovulation (indicated by ultrasound scan and/or serum progesterone > 16 mmol/l) within 3 weeks in 93.6% and 90.9% of women after Implanon and Norplant removal, respectively.[355*] [EL = 1–]

One cohort study reported a cumulative pregnancy rate of 76% and 70% in ex-Norplant users (n = 51) and ex-DMPA users (n = 47), respectively, at 1 year. The corresponding figures were 90% and 89% at 2 years.[336] [EL = 2–]

Another cohort study reported that pregnancy occurred in 96% of ex-Norplant users (n = 87) compared with 100% of ex-users of copper IUDs (dose not stated) (n = 44) at 2 years.[398] [EL = 2–]

A questionnaire survey of pregnant women (n = 2841) in the UK evaluated the impact of contraceptive methods on subsequent fecundity. Conception rates within 6 months of discontinuation were 71%, 77%, 27% and 25% among users of COC (n = 925), IUDs (n = 82), injectables (n = 62) and implants (n = 4), respectively, compared with 82% among condom users.[209] [EL = 3] (See Sections 4.8, 5.8 and 6.7.)

SUMMARY OF EVIDENCE

- There is evidence of a rapid return to ovulation following removal of contraceptive implants.
- There is no evidence of delayed return to fertility for Implanon. The evidence for Norplant demonstrates no delay in the return of fertility. The GDG considered it appropriate to extrapolate.

RECOMMENDATION

Women should be informed that there is no evidence of a delay in the return of fertility following removal of contraceptive implants. **C**

7.8 Details of method use

Assessment prior to insertion

(See Section 3.6 for recommendations.)

The UKSPR recommends that blood pressure screening is desirable before initiation of contraceptive implants.[79] [EL = 1–4]

Information prior to insertion

RECOMMENDATIONS

Women should be informed about failure rates, benefits, risks and side effects of contraceptive implants. **D(GPP)**

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

Time of insertion of implants

In a normal menstrual cycle

Guidance from the UKSPR states that implants may be inserted at any time, if it is reasonably certain that the woman is not pregnant. If the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be advised for 7 days following insertion.[399]

When switching method

The UKSPR recommends that contraceptive implants can be inserted immediately if the woman has been using her hormonal methods consistently and correctly or if it is reasonably certain that she is not pregnant.[79] [EL = 1–4]

Following abortion

POSDI is assigned to category '1' for insertion for women after first- or second-trimester abortion in the current WHO-MEC recommendations.[63] [EL = 1–4] The RCOG abortion guideline recommends that any chosen method of contraception may be initiated immediately following abortion.[215] [EL = 1–4]

Post delivery

An analysis of the pharmacokinetics of Implanon reported that serum ENG levels increased within 8 hours after Implanon insertion to concentrations associated with ovulation inhibition.

Maximum mean serum concentration was reached after 4 days.[400,401] [EL = 3]

One RCT (n = 250) compared the safety and tolerance of Norplant when inserted immediately postpartum with insertion 4–6 weeks postpartum. The immediate insertion group reported significantly more bleeding days (28 ± 7.7 days versus 22 ± 7.3 days) and headaches, but there were no significant differences in haemoglobin values at 4–6 weeks postpartum between the two groups. These side effects did not appear to differ from those reported in a previous study.[402] [EL = 1–]

POSDI is assigned to category '1' for non-breastfeeding women (less and more than 21 days) postpartum in the current WHO-MEC recommendations.[63] [EL = 1–4] (See section 7.10.)

RECOMMENDATION

Healthcare professionals should be aware that, provided that it is reasonably certain that the woman is not pregnant, Implanon may be inserted:

D(GPP)

- at any time (but if the woman is amenorrhoeic or it has been more than 5 days since menstrual bleeding started, additional barrier contraception should be used for first 7 days following insertion)
- immediately after abortion in any trimester
- at any time postpartum.

Insertion and removal

We did not identify any studies which assessed the duration of Implanon insertion including consultation, insertion and women leaving the consulting room.

Complications of insertion and removal include pain at the site, physiological responses to a minor operation, and bruising. Complications at removal additionally include an inability to locate implants and broken implants. Since Norplant comprises six rods and Implanon only one, the incidence of problems associated in the insertion and removal is lower for Implanon. A meta-analysis of clinical trials reported complications at insertion and removal of 0.3% versus 0% and 0.2% versus 4.8% for Implanon and Norplant, respectively. Pain at the insertion site was the most frequently reported symptom, with incidences of 0.9% and 1.9% in the Implanon group and Norplant group, respectively.[360] [EL = 1–]

Implanon was associated with a significantly lower frequency of removal complications when compared with Norplant (0.2% versus 4.8%).[355*,360*,403*] [EL = 1–]

Complications in the Implanon group included six deep insertions, six with fibrous adhesions, four where there was difficulty finding the implant and three broken implants. In the Norplant group, four were broken implants, two were difficult to find and one was time-consuming. There was no report of expulsion of the device in the Implanon group and one reported expulsion with the Norplant group.[356*] [EL = 1–]

SUMMARY OF EVIDENCE

- The risk of local discomfort and pain at insertion or removal is infrequent and is less than 1% for Implanon. Broken or non-palpable rods complicating removal occur less frequently with Implanon than Norplant (0.2% compared with 4.8%).
- Immediate postpartum insertion of Norplant resulted in more bleeding days and headaches compared with delaying insertion to 4–6 weeks.

RECOMMENDATION

Women should be informed that if an Implanon implant cannot be palpated (due to deep insertion, failed insertion or migration) it should be localised by ultrasound investigation before being removed. Deeply inserted implants often need to be removed by an expert.

D(GPP)

7.9 Training of healthcare professionals

(See Section 3.14.)

The FFPRHC provides training for healthcare professionals wishing to obtain the letter of competence (LoC) in subdermal contraceptive implant techniques. Adequate experience will be deemed to consist of a minimum of two insertions and two removals of subdermal implants over the 5 year recertification period.[404]

RECOMMENDATION

Contraceptive implants should be inserted and removed only by healthcare professionals trained in the procedure. **D(GPP)**

7.10 Specific groups

Adolescents

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

Women over 35 years of age

A non-comparative study (n = 53) in Thailand assessed the use of Implanon in women over 35 years of age (mean age 39.7 years, mean BMI 24.9 ± 3.3 kg/m^2) over 6 months. It reported no pregnancy. The most common side effects reported were irregular bleeding (53%) and amenorrhoea (35%). Regular cycles were reported in 11% of Implanon users. There was no change from baseline in diastolic pressure, body weight or BMI. The discontinuation rate was 8% at 6 months.[405] [EL = 3]

Adolescents versus adults

A cohort study (n = 678) comparing side effects and acceptability between adolescent users (13–18 years) and adult users (19–46 years) of Norplant reported no method failures in either group. There was no significant difference in concerns about irregular bleeding requiring clinic visits (57% of adolescents versus 38% of adults). The most common reason for implant removal was irregular bleeding (6% of adolescents versus 3% of adults). The overall cumulative discontinuation rates were 8% and 10%, respectively, at 1 year and 11% in both groups at 18 months.[406] [EL = 2+]

Another cohort study (n = 1688, 45 576 woman-months) reported no significant difference in cumulative discontinuation rates between adolescent users (n = 674) and adult users (n = 1014) of Norplant at 50 months. There were no significant differences in the primary reason for implant removal between the two groups (irregular bleeding 28%, headaches 20% and local arm irritation or pain 16%). There were two pregnancies (failure rate of 0.11%), but it was not clear in the study in which group the pregnancies occurred.[407] [EL = 2+]

Norplant versus other contraceptive methods

A case–control study (n = 112) which compared adolescents (11–18 years) who used Norplant or COC reported significant differences in the pregnancy rate (0% versus 25%) and discontinuation rate (9% versus 66%) at 12 months follow-up. Menstrual irregularity occurred significantly more often among Norplant users than COC users (73% versus 5%). No significant difference was detected between Norplant and COC users in the reporting of weight gain (60% versus 53%), headaches (26% versus 42%), emotional problems (26% versus 5%) or amenorrhoea (6% versus 0%). Objective measurements of weight and body mass index showed weight gain in both groups (4 kg in Norplant users versus 2 kg in COC users) at 12 months. Weight gain in excess of 9.1 kg was limited to Norplant users.[408] [EL = 2–]

A cohort study (n = 166) in the USA reported a significant difference in pregnancy rates among adolescents (12–18 years) who were using Norplant, COC or other methods (condoms or no methods) (2% versus 13% versus 17% during the 1 year study period). Norplant users were

significantly more likely to continue with the method than COC users (87% versus 50%) despite similar satisfaction scores at 6 months. There were significant differences between Norplant and COC users and other methods (condoms or no methods) in reports of irregular bleeding (89% versus 59% versus 54%), headaches (39% versus 37% versus 10%), mood swings (54% versus 32% versus 25%), acne (30% versus 12% versus 10%) and hair loss (15% versus 0% versus 0%). The difference in weight gain was not significant (52% versus 40% versus 42%). The most common reason given for discontinuing Norplant was menstrual irregularity (71%).[409] [EL = 2–]

One US cohort study that compared Norplant (n = 58) with DMPA (n = 66) and COC (n = 75) in adolescent users (11–20 years) reported no differences between the three groups in headaches, depression, acne or weight gain. Over 80% of DMPA and Norplant users reported irregular menstrual bleeding whereas 90% of COC users experienced regular cycles at 6 months.[291] [EL = 2–]

A cohort study (n = 48) of adolescents (12–21 years) reported no significant differences in BMD among Norplant users, DMPA users, OC users and controls (no hormonal methods) at 1 year. There were significant differences in BMD among the groups at 2 years (a total increase of 9.3% in Norplant users, a total decrease of 3.1% in DMPA users and a total increase of 9.5% in the controls).[320] [EL = 2–]

A cohort study (n = 98) amongst postpartum adolescent mothers (at or under 17 years) in the USA reported that the main reasons for choosing Norplant were difficulty remembering to take the pills (71%), side effects of OC (38%), fear of pregnancy (57%), ease of use of Norplant (48%) and encouragement from others (34%). Seventy-four percent of Norplant users were 'very satisfied' with the implant and 95% would recommend its use as compared with 38% and 79%, respectively, in the OC users. There was a significant difference in discontinuation rates (5% in Norplant users versus 33% in COC users) at 15 months.[410] [E=2–]

A US questionnaire survey (n = 112) of adolescents (13–20 years), including mothers, reported a high level of interest (over 70%) in Norplant because of its contraceptive effectiveness and convenience. The most undesirable side effects were acne, headaches, weight changes and menstrual changes, reported by 87%, 83%, 71% and 71% of the adolescents, respectively. One prior pregnancy was the main characteristic predictive of a high level of interest in Norplant.[411] [EL = 3]

Norplant is assigned to category '1' for women aged under 18 in the current WHO-MEC recommendations.[63] [EL = 1–4]

SUMMARY OF EVIDENCE

- There is no evidence for any difference in side effects or reasons for discontinuation among adolescents compared with adults.
- There is evidence for lower pregnancy rates in adolescents compared with use of pills and condoms.
- There is no evidence for differences in effectiveness or adverse effects between different age groups

RECOMMENDATION

Women should be informed that there is no evidence that the effectiveness or adverse effects of implants vary with the age of the user. **C**

Women with body mass index over 30 kg/m^2

There have been concerns that the efficacy of some progestogen-only methods may be compromised in heavier women.

A meta-analysis of clinical trials reported no pregnancies among Implanon users weighing ≥ 70kg at 1 year (n = 161), 2 years (n = 125) and 3 years (n = 78).[355*] [EL = 3] However, the numbers in these trials were small.

Implanon is assigned to category '1' for women with BMI ≥ 30 kg/m^2 in the current WHO-MEC recommendations.[63] [EL = 2–]

SUMMARY OF EVIDENCE

- From small studies, there is no decrease in efficacy for Implanon for women who weigh more than 70 kg.

RECOMMENDATION

Healthcare professionals should be aware that women over 70 kg can use Implanon as an effective method of contraception. **D(GPP)**

Women who are breastfeeding

(Refer to Section 7.8 – Time of insertion of implants.)

Concern has been raised that hormonal methods of contraception interfere with milk production and have adverse effects on the baby.

A cohort study compared changes in the volume and composition of breast milk in breastfeeding women who elected to use Implanon (n = 42) or nonhormonal IUD (n = 38) at 6 weeks postpartum. There were no significant differences between the two groups in the changes in milk content of fat, protein and lactose.[412] [EL = 2–]

A cohort study (n = 108) reported that initiation of Norplant in healthy lactating women around day 60 postpartum had no deleterious effect on bone density measurements when compared with users of copper T 380A IUD and/or progesterone-releasing vaginal rings at 1 year during lactation and 1 year after weaning.[413] [EL = 2+]

Beyond 6 weeks postpartum, Implanon is assigned to category '1'. Up to 6 weeks postpartum WHO-MEC considers Implanon to be in category '3'.[63] The FFPRHC does not support the latter view and recommends using local guidelines.

SUMMARY OF EVIDENCE

- The evidence does not support the concerns that hormonal methods of contraception interfere with milk production and have adverse effects on the baby.

RECOMMENDATION

Healthcare professionals should be aware that contraceptive implants can safely be used by women who are breastfeeding. **C**

7.11 Medical conditions and contraindications

Diabetes

Women with diabetes are at increased risk of cardiovascular disease. Concerns about the effects on the cardiovascular system and on carbohydrate metabolism often deter doctors from prescribing hormonal methods of contraception.

We did not identify any studies which assessed the effect of Implanon use on women with diabetes.

A cohort study (n = 80) compared glycaemic control, lipoprotein metabolism and coagulation profile in diabetic women using Norplant, DMPA, COC or IUD. It reported minimal alterations in Norplant users. There were small changes among COC users but the most significant changes occurred among users of DMPA.[232] [EL = 2–]

Norplant and Implanon are assigned to category '1' for women with a history of gestational disease, and to category '2' for women with insulin- and non-insulin-dependent diabetes in the current WHO-MEC recommendations.[63] [EL = 2–]

SUMMARY OF EVIDENCE

- There is no evidence of a significant disturbance to diabetic control in women using Norplant.

Epilepsy

A systematic review (one cohort study and two case reports) conducted to update the WHO-MEC reported conflicting evidence on the safety of concurrent use of an anti-epileptic drug and hormonal contraceptive methods. However, no harmful effect on epilepsy or seizure frequency was reported in this cohort study.[414,415] [EL = 2–]

Sexually transmitted infections, HIV and AIDS

(See Section 3.11)

A systematic review (two non-comparative studies) conducted to update the WHO-MEC reported that, in postpartum Norplant users with asymptomatic HIV-1 infection, the side effect profiles are similar to those reported in other studies of non-infected women. No measures of disease progression were reported in these studies.[233] [EL = 3]

Norplant and Implanon are assigned to category '1' for women who are HIV-positive or with high risk of HIV in the current WHO-MEC recommendations.[63] [EL = 2–]

RECOMMENDATION

Healthcare professionals should be aware that:

D(GPP)

- Implanon use is not contraindicated in women with diabetes
- there is no evidence that implant use increases the risk of STI or HIV acquisition
- contraceptive implants are a safe and effective method of contraception for women with STI, including HIV/AIDS (safer sex using condoms should be encouraged in this group).

7.12 Drug interactions

Some drugs, in particular certain anti-epileptic drugs, induce liver enzymes and thereby hasten the metabolism of steroid hormones. This has the effect of reducing serum levels and in the case of contraceptive steroids this may lower contraceptive efficacy (see Section 7.11).

We did not identify any studies which assessed drug interactions among Implanon users.

A systematic review (one cohort study and two case reports) conducted to update the WHO-MEC reported conflicting evidence on the safety of concurrent use of an anti-epileptic drug and hormonal contraceptive methods. The majority of the studies reviewed were methodologically flawed with small sample size. Lower LNG serum levels and contraceptive efficacy were reported after Norplant insertion in women taking the anti-epileptic drugs phenytoin and carbamazepine, suggesting that Norplant may not be reliable in patients taking phenytoin and carbamazepine.[414,415] [EL = 2–]

Norplant and Implanon are assigned to category '3' for women taking the enzyme-inducers phenytoin, carbamazepine, barbiturates and primidone in the current WHO-MEC recommendations.[63] [EL = 1–4]

Theoretical concerns exist about interactions between hormonal contraceptives and antiretroviral drugs. It is possible that the efficacy of both groups of drugs may be reduced. A systematic review undertaken by the WHO-MEC concluded that insufficient published data exist to allow any recommendation to be made about the concurrent use of hormonal contraceptive and antiretrovirals.[76] [EL = 1–4]

SUMMARY OF EVIDENCE

- Contraceptive implants may be associated with higher failure rates in women concurrently taking hepatic enzyme-inducing drugs. **D**

RECOMMENDATION

Healthcare professionals should be aware that Implanon is not recommended as a contraceptive method for women taking liver enzyme-inducing drugs.

7.13 Follow-up

The UKSPR recommends that no routine follow-up visit is required once Implanon has been inserted. Healthy implant users are advised to return at any time to discuss side effects or other problems, or if they want to change the method, and to return when it is time to have the implant removed.[79] [EL = 1–4]

RECOMMENDATION

Healthcare professionals should be aware that no routine follow-up is needed after implant insertion. However, a woman should be strongly encouraged to return at any time to discuss problems, if she wants to change her method of contraception, or if it is time to have the implant removed. **D(GPP)**

8. Economic evaluation

8.1 Introduction – the role of health economics in this guideline

The aim of the economic evaluation was to assess the cost effectiveness of long-acting reversible contraceptive (LARC) methods. Estimation of cost effectiveness of LARC methods was regarded as an important piece of information, especially for healthcare providers, as the high initial costs associated with most LARC methods (in particular the IUS and the implant) were believed to be among the main barriers to the availability of LARC methods in the NHS, contributing to their current low uptake.

Cost effectiveness of LARC methods was evaluated in comparison with the combined oral contraceptive pill (COC), the male condom, and also non-reversible contraceptive methods, i.e. female and male sterilisation. The COC and non-reversible contraceptive methods were selected as comparators by the Guideline Development Group (GDG), with the justification that women of reproductive age who are likely to consider (and substantially benefit from) LARC as a contraceptive option are mainly those already using the COC, or those considering COC/non-reversible contraception as an alternative method. The male condom was chosen on the basis that it is the second most common method of contraception after oral contraceptives in the UK.[1] In addition, the relative cost effectiveness between different LARC methods was explored.

In order to assess the cost effectiveness of LARC methods a systematic literature review was undertaken, along with a cost effectiveness analysis based on a decision-analytic model that was developed for this purpose. The results of the literature review are presented first, focusing on the content, findings and limitations of UK-based studies. Then a description of the economic model used in the guideline is provided, including details on the rationale for the model, cost and effectiveness parameters considered, the design of the model, and the input values used. Finally, the results of the cost effectiveness analysis are presented accompanied by evidence statements.

8.2 Literature review

The systematic search of the literature identified 1083 studies potentially related to the economic question. All paper abstracts were reviewed, and 24 articles were retrieved and critically appraised. Fourteen articles were finally included in the review as relevant to the economic question. Eight of the studies were conducted in the USA[416–423] and one in Thailand.[424] The general conclusion drawn by these studies was that all contraceptive methods provided substantial cost savings compared with no method.[416–420] Female and male sterilisation were shown to be the most cost effective methods (highest level of effectiveness at lowest cost) in the long term.[419,421,422] LARC methods were also highly cost effective, especially IUDs and the IUS, followed by the injectable and the implant.[419–422] Two studies that assessed the cost effectiveness of the implant showed that this depended significantly on the duration of use of the method.[423,424] However, the above results refer to the specific context in which the studies were conducted. The healthcare systems of the USA and Thailand differ from that of the UK in terms of organisation, access and resource use, and therefore conclusions derived from non-UK studies are of limited value in the UK context.

Five studies (one of which was an update of an earlier study using the same methodology) were conducted in the UK, and published from 1995 to 2004.[126,425–428] Although in the majority they may have utilised non-UK effectiveness data, they were nevertheless considered relevant to the UK context, since they were based on UK resource use patterns and unit prices. The methodology and results of these studies were used to inform the economic model developed

for this guideline. Each study included an economic model, which incorporated effectiveness rates and costs associated with events related to contraceptive use, in order to estimate the relative cost effectiveness of various contraceptive methods. All five studies adopted the NHS perspective. Table 8.1 shows the types of cost and effectiveness variables used in the economic models and the method of presentation of results in the UK-based studies.

Table 8.1 Categories of input parameters and method of presentation of results in UK-based studies

Study	Methods examined	Viewpoint and costs included/excluded	Effectiveness	Results	Comment
Varney and Guest (2004)[428]	Comparisons between Implanon, IUS and injectable (DMPA)	NHS viewpoint; 2002/03 prices *Included:* • method costs • healthcare resource use: primary care and outpatients (including costs associated with discontinuation) • costs of unintended pregnancies (excluded from the cost effectiveness analysis; included only in a cost–benefit analysis) *Excluded:* • costs of further treatment of side effects (i.e. in addition to those associated with discontinuation) • costs of switching to a new method after discontinuation	Number of pregnancies averted	• Additional cost per additional pregnancy averted (incremental analysis) • Net cost–benefit analysis	• Cost estimates based on actual resource use data, derived from a GP database • Direct comparisons between the methods examined
Phillips (2000)[425]	Implanon compared with Norplant and Mirena; further comparison with DMPA and COC	NHS viewpoint; 1997/98 prices *Included:* • method costs adjusted for discontinuations • savings due to pregnancies averted (compared with no method) *Excluded:* • costs associated with side effects	Number of pregnancies averted compared with no method	• Net savings per patient • Method costs per pregnancy averted, abortion averted, protected year • Additional cost per additional pregnancy averted in comparisons with DMPA and COC (incremental analysis)	• Comparisons between each method and no method • Direct comparisons only between Implanon and DMPA, and between Implanon and COC
McGuire and Hughes (1995)[426]; Hughes and McGuire (1996)[427]	Contraceptive methods available in the UK: condom, spermicide, diaphragm, OC, injectable, IUD, implant, vasectomy, female sterilisation	NHS viewpoint; 1991 prices *Included:* • method costs • savings due to pregnancies averted (compared with no method) *Excluded:* • costs associated with side effects and discontinuations	Number of pregnancies averted compared with no method	• Net savings per pregnancy averted • Net savings per adjusted couple-year of protection	• Comparisons between each contraceptive method and no method
French *et al.* (2000)[126]	Norplant compared with: IUD > 250 mm^2, IUD ≤ 250 mm^2, OC, DMPA. Mirena compared with: IUD > 250 mm^2, IUD ≤ 250 mm^2.	NHS viewpoint; 1998 prices *Included:* • method costs (ingredient and health service resource use) • failure costs (associated with pregnancy outcomes) *Excluded:* • costs associated with side effects and discontinuations	Number of pregnancies averted	• Additional cost per additional pregnancy averted (incremental analysis)	• Effectiveness rates based on a systematic review and meta-analysis • Direct comparisons between the methods examined

Costs included and excluded in the UK-based studies

All UK studies included contraceptive method costs (ingredient costs and health service costs). They also considered the costs to the health service associated with outcomes of unintended pregnancies due to contraceptive failure, i.e. live births, miscarriages and abortions. In some cases these costs were expressed as savings from unintended pregnancies averted by contraceptive use. The study by Varney and Guest[428] did not include this category of costs in the cost effectiveness analysis, with the justification that this type of cost was not part of the interventions. Nevertheless, the cost associated with an unintended pregnancy resulting from contraceptive failure was incorporated in an additional net cost–benefit analysis provided.

Other costs to the public purse, such as social service expenditure and welfare payments, as well as costs to the women, were not included in the cost effectiveness analyses. Costs incurred during the life of a person born as a result of contraceptive failure were not taken into account. In addition, adverse events and secondary beneficial effects of contraception were, in principle, not considered in the studies; however, Varney and Guest utilised actual resource use data (GP and practice nurse visits, as well as referrals to a gynaecologist outpatient clinic) in order to estimate total costs associated with contraceptive use. Therefore, management of some side effects (such as those that did not require additional treatment, e.g. hospitalisation) was reflected in total cost estimates.

Costs associated with discontinuation of a method were taken into account in two of the UK-based studies.[425,428] These costs refer to costs of starting a new contraceptive method following discontinuation of a previously chosen one (additional consultations with healthcare professionals and start-up costs) and costs associated with unintended pregnancies resulting from subsequent use of a possibly less effective contraceptive method (or no method). The Philips study[425] estimated costs associated with premature withdrawal of a method (discontinuation) and switching to other contraceptive methods, based on reported switching patterns for contraceptive users. Costs included start-up costs, costs reflecting additional healthcare resource use, and costs associated with unintended pregnancies following discontinuation. The Varney and Guest analysis[428] incorporated resource utilisation data for women discontinuing one of the contraceptive methods examined. However, costs associated with switching patterns of these women (i.e. start-up costs of a new method used following discontinuation of the initially started method) were not included in the analysis, as no relevant information was available.

Outcomes measured in the UK-based studies

The main measure of effectiveness was the number of pregnancies averted by one method compared with no method[425–427] or with another contraceptive method.[126,428]

Preferences attached to different forms of contraception and issues related to quality of life were not examined in the studies reviewed. Moreover, issues concerned with the valuing of life foregone by contraceptive use, or life resulting from an unintended pregnancy that continues to live birth (for both the pregnant woman and the baby born), were not considered in these studies.

Presentation of the results

The cost effectiveness results of the studies were reported using two different methodologies:

1. In the report by McGuire and Hughes[426] and in their updated study,[427] results were presented as net savings (to the NHS) per pregnancy averted or per adjusted couple-year of protection. These represented the actual savings to the NHS (savings from pregnancies averted minus method costs of contraception) associated with preventing one pregnancy by using a contraceptive method. In the study by Philips,[425] results from the main comparisons (between two types of implant and the IUS) were presented as net savings per woman provided with a contraceptive method, and also as method costs per pregnancy averted, per abortion averted, and per protected year, for each of the contraceptive methods assessed. In all cases contraceptive methods were implicitly compared with a 'no method' alternative. Therefore, all net savings per unit of effectiveness referred to the economic benefits of each contraceptive method examined against no method of contraception. Direct comparisons between the two types of implant and the IUS were not

performed, i.e. the additional costs and benefits of switching between these methods were not examined.

2. French *et al.*[126] and Varney and Guest[428] reported the results as additional costs per additional pregnancy averted (incremental cost effectiveness ratio) from switching between contraceptive methods, thus allowing for direct comparisons between different methods. Philips also used this methodology for a part of the analysis that directly compared Implanon with injectable and the COC.[425]

Overall findings from the UK-based literature

McGuire and Hughes[426,427] showed that all methods of contraception were cost effective, providing net savings per pregnancy averted or per couple-year of protection. However, the value of this analysis is limited in the context of this guideline as it does not allow for direct comparisons between contraceptive methods so that their relative cost effectiveness can be assessed. Such an analysis is required in order to explore the resource consequences of switching between contraceptive methods that may differ in effectiveness but also in associated costs.

French *et al.*[126] performed comparisons between different methods of contraception. The number of comparisons was limited since the effectiveness analysis was based on a systematic review and meta-analysis of studies meeting strict inclusion criteria. The main comparators were subdermal implants (Norplant) and the IUS (Mirena). All comparisons showed that there were additional costs (ranging from £721 to £255,102) per pregnancy averted associated with switching to Norplant or Mirena from any other contraceptive method included in the analysis.

The study by Varney and Guest[428] made direct comparisons between the implant, the IUS and the injectable. The analysis demonstrated that the injectable was dominated by both the implant and the IUS (i.e. it was less effective and more costly than the implant and the IUS). The implant was more effective than the IUS, but at an additional cost of £20,953 per pregnancy averted; the authors concluded that the implant was likely to be less cost effective than the IUS, as they considered the additional cost per additional pregnancy averted relatively high, compared with the cost of an unintended pregnancy to the NHS (£912). It is noted that this incremental cost effectiveness ratio between the implant and the IUS (£20,953 per pregnancy averted) did not include costs of events resulting from unintended pregnancies due to contraceptive failure (i.e. live birth, abortion or miscarriage). Additional probabilistic analyses (obtained by performing Monte Carlo simulations), undertaken to explore the robustness of the above results under the variability and uncertainty of the model input parameters, showed that the probability of the implant and IUS being the dominant options compared with the injectable was >90%. In contrast, the likelihood of the incremental cost effectiveness ratio between the implant and the IUS being below the cost of an unintended pregnancy was only 19%. Finally, a net cost–benefit analysis, which included the cost of an unintended pregnancy due to contraceptive failure, demonstrated that the annual net cost benefit to the NHS of using IUS, implant and injectable compared with no use of contraception was £18, £12 and £6 per woman, respectively.

The Philips study[425] demonstrated that LARC methods provided effective contraceptive protection and represented value for money from the perspective of the healthcare service. Implanon was reported to be more cost effective than Norplant and Mirena in terms of method cost per pregnancy averted and method cost per protected year; however, no direct comparisons were performed between these methods. The direct comparison between Implanon and DMPA demonstrated that Implanon was both less costly and more effective. Finally, compared with COC, Implanon incurred an additional method cost of £616 per additional pregnancy averted (in this case costs associated with discontinuation of COC were not taken into account).

Limitations of UK-based literature

The UK-based studies are characterised by a number of limitations regarding the design of the economic models. The models did not always incorporate events such as discontinuation of contraceptive method (this was considered only by Philips[425] and Varney and Guest[428]) and adverse events (this was incorporated partially in the study by Varney and Guest,[428] in which some costs of treating side effects were included). Both types of events are regarded as important parameters in the use of LARC methods, which may affect their relative cost effectiveness.

In the context of LARC method use, discontinuation of a method is an important issue since it is likely to lead to the use of a less effective method or no use of contraception and consequently to more unintended pregnancies. Moreover, methods with a long duration of effectiveness that carry relatively high initial costs, such as the implant, the IUS or the IUDs, require a substantial period of use so that their higher level of effectiveness in the longer term offsets their initial costs. For these reasons, and since it was found that LARC methods were related to high discontinuation rates, the omission of discontinuation rates in the estimation of cost effectiveness of LARC methods was considered to be a limitation of some of the UK studies.

Adverse effects may also have an impact on the relative cost effectiveness of LARC methods if they lead to additional healthcare resource use (e.g. additional GP consultations or hospitalisation required for management). Nevertheless, costs associated with management of side effects of contraceptive use were also not considered in the majority of the UK studies.

Finally, direct comparisons between contraceptive methods were limited in this literature. Therefore, the impact of switching from one contraceptive method to another in terms of incremental costs to the NHS and contraceptive benefits to the users was not investigated.

8.3 Development of a model for the economic evaluation of LARC methods

Rationale for the model

An economic model was developed in order to examine the cost effectiveness of LARC methods based on the clinical effectiveness data presented in this guideline. Direct comparisons were made across different LARC methods, and also between LARC methods and other forms of contraception that the GDG considered as relevant alternatives to LARC methods: the COC, the male condom, and non-reversible methods (female and male sterilisation). Consequently, the economic analysis undertaken for the guideline examined the relative cost effectiveness of switching from one contraceptive method to another. The cost effectiveness of using a specific contraceptive method versus use of no method was not determined.

The economic model was intended to overcome some of the limitations identified in the previously published studies, by incorporating parameters such as discontinuation rates and frequency and cost of side effects of contraceptive use, which were thought to affect the relative cost effectiveness between contraceptive methods. In the case of side effects, estimation of management costs was not feasible, as there were no reliable data on the frequency of side effects that required additional healthcare resource use (e.g. GP consultations and inpatient care), and the associated costs of clinical management. It is recognised that omission of costs associated with the management of side effects from the model structure constitutes a limitation of the analysis. Nevertheless, it was possible to include discontinuation rates in the development of the economic model, based on data reported in the guideline. Although not all side effects lead to discontinuation, and, conversely, not all discontinuations occur as a result of side effects, it is well established that a significant proportion of discontinuations are due to side effects, and in this sense the incidence of side effects following contraceptive use was partially reflected in discontinuation rates. Thus, the relative cost effectiveness between contraceptive methods was determined not only by clinical effectiveness, but also by the rates of discontinuation characterising each method.

Finally, an update of cost and effectiveness data was considered useful, since some of the UK studies were based on data collected up to 10 years ago.

Cost and outcome parameters considered in the model

The perspective adopted in the economic analysis was that of the NHS. Costs included in the model consisted of method costs (ingredient and health service costs) as well as costs due to contraceptive failure (unintended pregnancy and its consequences). Costs associated with clinical management of adverse effects were not considered in the analysis, since no relevant data could be identified in the published literature.

Non-contraceptive beneficial effects and associated cost savings (e.g. the reduction in need for surgical treatment of menorrhagia following IUS use[429] and the protective role of male condom against sexually transmitted infections) were not considered in the estimation of costs, as relevant data were difficult to identify because beneficial non-contraceptive effects were not included in the scope of the guideline.

The societal costs incurred by unintended pregnancies (e.g. income maintenance payments and costs of adoptions arising from unintended pregnancies) and indirect costs (productivity losses) were not examined in the economic model. The long-term costs and consequences arising from raising a child born as a result of an unintended pregnancy were beyond the scope of the guideline. Moreover, it would be necessary to consider both the future costs *and* benefits for the evaluation to be meaningful, and no straightforward and satisfactory way of identifying and measuring the future costs and benefits to society (associated with the termination of an unintended pregnancy or with a live birth resulting from it) was available to inform the analysis. Similarly, issues concerned with the value of life foregone by contraceptive use, or life resulting from unintended pregnancy, were not considered in the economic analysis.

The costs of unintended pregnancy were estimated up to the birth of a viable baby (i.e. including costs of neonatal care until discharge of the infant from hospital). All pregnancies were assumed to be unintended; no distinction was made between unwanted and unplanned pregnancies (in some of the published literature unintended pregnancies were divided between unwanted pregnancies that would never occur later in time, and unplanned or mistimed pregnancies that would occur sometime later in the future[430–433]). This classification has been used mainly in non-UK economic studies on contraception for the estimation of cost savings due to contraceptive use. In the case of unwanted pregnancies, cost savings included the total cost of an unwanted birth, whereas in the case of unplanned pregnancies cost savings were lower, and they occurred only because the cost of an unplanned birth was deferred to a later time (when pregnancy was planned).[416,417,419] However, the GDG expressed the opinion that both unwanted and unplanned births often result in an ultimate increase in the number of children in the family (i.e. an 'unplanned' child born earlier than a woman/couple plans to have children usually does not reduce the number of 'planned' children born in the future). Therefore, unwanted pregnancies were not distinguished from unplanned pregnancies in terms of associated costs of birth, and the total costs of unintended births were included in the model.

Outcomes were expressed as the number of pregnancies averted by the use of one contraceptive method in comparison with another. The quality of life and users' preferences related to contraceptive use were not included in the model owing to lack of reliable data in the relevant literature.

Design of the model – basic assumptions

A decision-analytic Markov model was constructed in order to evaluate the cost effectiveness of LARC methods. This type of model was considered appropriate as it allowed for a dynamic representation of possible events associated with use of a contraceptive method, i.e. contraceptive failure and pregnancy, discontinuation and switching to another contraceptive method/no method, or a combination of these events. Additionally, such an approach allowed for the evaluation of cost effectiveness of LARC over various time frames.

The model was run in yearly cycles to assess whether the relative cost effectiveness between methods changed over time. A hypothetical cohort of 1000 sexually active women of reproductive age adopted one contraceptive method at the beginning of the first year. The model was constructed so that every year a proportion of women discontinued the method and chose another method or no method, represented by the concept of the 'average contraceptive method'. This concept was developed in order to consider the impact on cost effectiveness of discontinuation itself rather than of the patterns related to contraceptive method switching. In addition, there were no comprehensive data on switching patterns for LARC methods in the UK context. A limitation of this approach is that it did not consider the fact that women who discontinue one method are not always eligible to use all other methods available. Women discontinuing IUD, for example, may not be able to use hormonal methods due to contraindications (which may have led to the use of an IUD in the first place).

The average contraceptive method included all available contraceptive methods used in England and Wales. A weighted average failure rate was calculated taking into account failure rates for all contraceptive methods included, weighted by percentages of usage, derived from the most recent data on contraceptive usage in England and Wales for women 'at risk of pregnancy'.[1,434] Where failure rates were not reported in the guideline, these were derived from a published review.[435] A weighted average method cost was calculated using the same approach.

Every year, each member of the hypothetical cohort of women faced two possible events:

- contraceptive protection
- contraceptive failure and subsequent unintended pregnancy.

Four possible outcomes of unintended pregnancy were considered in the model:

- live birth
- miscarriage
- abortion
- ectopic pregnancy.

The probabilities of ectopic pregnancy resulting from contraceptive failure were specific to each method assessed. The relative probabilities of the remaining outcomes were assumed to be common for all methods. Note that the proportion of ectopic pregnancies among **unintended pregnancies** due to contraceptive failure associated with some methods (IUS, IUD and female sterilisation) is higher than the respective proportion in the general population, thus affecting the results in terms of associated costs.

The following costs were estimated in the model:

- method costs based on ingredient costs and healthcare resource use
- costs due to unintended pregnancy, related to all possible outcomes.

Outcomes were expressed as the number of unintended pregnancies due to contraceptive failure.

It was assumed that potential discontinuation of a LARC method and switching to the average contraceptive method occurred in the middle of each year, i.e. at 6 months. For the first 6 months, costs and contraceptive failure were attributed to the LARC method examined. For the remaining 6 months of the year (assumed to follow discontinuation), costs and contraceptive failure referred to the average contraceptive method.

The analysis considered multiple time horizons, starting from 1 year to 15 years of contraceptive use. The time horizon of 15 years was selected for the comparison between LARC and non-reversible contraceptive methods (i.e. female and male sterilisation), as this was estimated to be the average duration of effect of female sterilisation. The GDG felt that a comparison between LARC methods and female sterilisation should consider the full contraceptive benefit provided by female sterilisation. This time horizon was also applied to the comparisons between LARC methods and male sterilisation. Ultimately, the maximum time frame of 15 years of contraceptive use was also chosen for the rest of the comparisons performed in the analysis, i.e. between LARC and other reversible contraceptive methods (COC and the male condom) as well as across LARC methods.

A schematic diagram showing the structure of the decision-analytic model used for the economic analysis is presented in Appendix B.

Contraceptive methods examined in the model

The LARC methods evaluated in the economic analysis were:

1. IUD: The analysis was based on T-Safe CU 380A use (regarding cost and effectiveness data utilised). The analysis considered a maximum duration of use equal to 8 years. However, a sensitivity analysis (see below) investigated the impact on the results of a 5 year maximum duration of use. This was decided because, although T-Safe CU 380A is licensed for 8 years, other IUDs have a 5-year licensed duration of use.

2. IUS: LNG-IUS (Mirena).
3. Injectable: The analysis was based on DMPA use.
4. Implant: Implanon is the only implant currently available in the UK market and therefore this form of implant was examined in the model.

The comparators of LARC methods included in the analysis were the COC, the male condom, and female and male sterilisation. Because many different brands of COC are available in the UK market, an 'average' COC use was assumed (in terms of cost), based on prescription data for COC use in England in 2002.[436]

Cost data

Cost data associated with non-reversible contraceptive methods (female and male sterilisation) and events following contraceptive failure (live birth, miscarriage, abortion and ectopic pregnancy) were based on 2004 NHS reference costs,[437] owing to lack of research-based data. Ingredient costs were derived from the *British National Formulary 49*, March 2005.[122] Regarding health service costs related to contraceptive provision, the GDG estimated that these ought to be the same regardless of the provider of contraception, i.e. family planning clinics or GPs. It was decided that the estimation of health service costs be based upon GP contraceptive provision since data on GP unit costs were available and the respective resource use could be estimated by the GDG. In contrast, all cost data available for family planning clinics incorporated costs of providing services other than contraception, and specific costs related to contraceptive provision could not be identified. It was intended that costs reflected actual resource use rather than financial flows to GPs, therefore no additional fees paid to GPs for provision of contraceptive services were considered. However, in the case of miscarriages treated in GP practices, associated costs were derived from the GP fee schedule[438] owing to lack of other resource use-based data.

Resource use with respect to contraceptive provision was based on the considered opinion of the GDG. Costs of sterile packs required at insertion and removal of some LARC methods were also based on GDG consensus. Unit costs of GP consultations for the year 2004 were derived from published literature.[439] All costs included in the analysis reflect 2004/05 prices.

Table 8.2 shows all cost data considered in the analysis, including contraceptive method costs and costs associated with the outcomes of unintended pregnancies (i.e. continuation of pregnancy and live birth, abortion, miscarriage and ectopic pregnancy). Contraceptive method costs are analysed in their cost components. Total method costs of each contraceptive method, consisting of ingredient and health service costs, are provided for various durations of contraceptive use (depending on method), so that comparisons between method costs of different methods are possible.

Table 8.2 Cost data included in the economic model

Procedure or event	Baseline value	Cost components and basic assumptions	
		Component	**Cost**
IUD method cost		Ingredient cost (T-Safe CU 380A)	£9.56 per device[122]
First year cost:	£133	Initial GP consultation, 20 min	£44.80
Total 5 or 8 year cost:	£159	Consultation for insertion, 18 min	£40.32
		Sterile pack for insertion	£18.20
		Follow-up routine consultation 3–6 weeks after insertion, 9 min	£20.16
		Consultation for removal, 10 min	£22.40
		Sterile pack for removal	£3.17
		Resource use and cost of sterile pack based on GDG consensus; GP unit cost = £2.24 per surgery/clinic minute, including direct care staff costs and qualification costs.[439]	
IUS method cost		Ingredient cost (Mirena)	£83.16 per device[122]
First year cost:	£207	Initial GP consultation, 20 min	£44.80
Total 5 year cost:	£232	Consultation for insertion, 18 min	£40.32
		Sterile pack for insertion	£18.20
		Follow-up routine consultation 3–6 weeks after insertion, 9 min	£20.16
		Consultation for removal, 10 min	£22.40
		Sterile pack for removal	£3.17
		Resource use and cost of sterile pack based on GDG consensus; GP unit cost = £2.24 per surgery/clinic minute.[439]	
Injectable method cost		Ingredient cost (DMPA)	£5.01 per dose[122]
Annual method cost		Initial GP consultation (first year), 20 min	£44.80
First year:	£144	Consultation for injection every 12 weeks, 8 min	£17.92
Following years:	£99		
3 year cost:	£342	Resource use based on GDG consensus; GP unit cost = £2.24 per surgery/clinic minute.[439]	
5 year cost:	£540		
8 year cost:	£837		
Implant method cost		Ingredient cost (Implanon)	£90.00 per device[122]
First year cost:	£175	Initial GP consultation, 20 min	£44.80
Total 3 year cost:	£230	Consultation for insertion, 16 min	£35.84
		Sterile pack for insertion	£4.40
		Consultation for removal, 22 min	£49.28
		Sterile pack for removal	£5.50
		Resource use and cost of sterile pack based on GDG consensus; GP unit cost = £2.24 per surgery/clinic minute.[439]	
COC method cost		Weighted average ingredient cost	£1.37 per month[122]
Annual method cost		Initial GP consultation (first year), 20 min	£44.80
First year:	£106	Two routine consultations per year, 10 min each	£44.80
Following years:	£61		
3 year cost:	£228	Resource use based on GDG consensus; weighted average price based on prescription data for	
5 year cost:	£350	COC use in England in 2002;[436] GP unit cost = £2.24 per surgery/clinic minute.[439]	
8 year cost:	£533		
Male condom method cost		Ingredient cost	£0.56 per item (retail price)
Annual method cost:	£29		
3 year cost:	£87	No GP consultation was considered in the calculation of method cost. It was assumed that 52	
5 year cost:	£145	condoms were used annually, based on the results of a Welsh survey of sexual attitudes and	
8 year cost:	£232	lifestyles.[447]	
Female sterilisation	£712	Average NHS reference cost for upper genital tract intermediate procedures (day cases),[437] adding an initial 20 min GP consultation cost. In case of contraceptive failure, repeat of the procedure was considered.	
Vasectomy	£455	It was estimated that two-thirds of vasectomies take place in GP practices and one-third in hospitals/community care settings.[434] A cost of £200 was agreed by the GDG for GP-undertaken vasectomies, including procedure and consultation costs, based on web sources. For hospital/community-based procedures a weighted average NHS reference cost (elective, non-elective, day cases and community-based services) was used,[76] adding an initial 20 min GP consultation cost. In case of contraceptive failure, repeat of the procedure was considered.	
Average contraceptive method		Weighted cost based on contraceptive usage rates in England and Wales for women 'at risk of pregnancy'.[1] Incidence rates rather than prevalence were used for female and male sterilisation.[434]	
Average annual cost:	£38	An initial 20 min GP consultation was assumed. Annual costs of female and male sterilisation	
Initiation:	£45	were estimated by dividing total costs by 15 years (average duration of effect on couple – GDG expert opinion). Additional ingredient costs for barrier methods were based on market retail prices.	

Table 8.2 Cost data included in the economic model (continued)

Procedure or event	Baseline value	Cost components and basic assumptions	
		Component	Cost
Total maternity cost:	£2,137	NHS reference cost, including cost of antenatal care, live birth, care of unhealthy neonates and NICU levels 1 and 2.[437]	
Cost of antenatal care:	£518	Total costs of antenatal clinics, outpatient obstetrics and community midwifery visits reported in the NHS reference costs were divided by the total number of births reported in the same document in order to estimate the cost of antenatal care per live birth.[437]	
Cost of live birth:	£1,170	Weighted average of normal deliveries, assisted deliveries and caesarean sections, treated as elective, non-elective and day cases or in community services.	
Cost of care for unhealthy neonates + NICU for unstable neonates (adjusted per live birth):	£449	Total costs of neonates that died within 2 days of birth or had one/multiple minor/major diagnoses, reported in the NHS reference costs, were added to the total costs of NICU levels 1 and 2, also reported in the NHS reference costs, and the sum was divided by the total number of live births provided in the same document.[437]	
Abortion:	£497	Weighted average NHS reference cost (surgical or medical termination of pregnancy, treated as elective, non-elective or day case).[437]	
Miscarriage:	£321	Weighted average NHS reference cost (elective, non-elective and day cases)[437] and GP fee for miscarriage (£77.50).[438] It was assumed that 30% of miscarriages were treated by GPs (GDG expert opinion).	
Ectopic pregnancy:	£1,398	Weighted average NHS reference cost (elective, non-elective and day cases) for upper genital tract intermediate procedures (reflecting laparoscopy), upper genital tract major procedures (reflecting laparotomy), and non-surgical treatment of ovaries, tube, pelvis disorders (reflecting medical treatment).[437] The relative weights used for the estimation of costs were based on Scottish data:[448] 58% of ectopic pregnancy management involved laparoscopy, 35% involved laparotomy, and 7% of ectopic pregnancies were medically managed.	

Effectiveness data and other input parameters of the model

Effectiveness rates for LARC methods were derived from the results of the systematic reviews undertaken for the development of the guideline. Annual rates of discontinuation were based on data reported in the guideline agreed by the GDG members, or, where evidence was limited, on GDG consensus. Probabilities of ectopic pregnancy resulting from contraceptive failure were also based on data presented in the guideline. The estimation of probabilities for the other outcomes of unintended pregnancy was based on national statistics,[440,441] a literature review on unintended pregnancy[430–433] and additional assumptions agreed with the GDG. Respective input data for the comparators (male condom, COC, female and male sterilisation) were derived from published literature.[435,442–445] All effectiveness data and other clinical input parameters included in the analysis are presented in Table 8.3.

Costs and outcomes occurring at a point in time later than 1 year from the start of the model were discounted at an annual rate of 3.5%, as recommended by NICE guidance on technology appraisal.[446] Discounting is a method of calculation by which costs and benefits of medical processes that occur at different times can be compared. The method converts the value of future costs and benefits into their present value, reflecting society's 'time preference' (e.g. present benefits are valued more highly than future ones).

Sensitivity analysis

In addition to the base-case analysis, which was based on the most accurate effectiveness and cost estimates available, a sensitivity analysis was performed. This analysis examined the robustness of the base-case results under the uncertainty characterising the input parameters. The impact of variability in effectiveness and discontinuation rates on the results was tested by varying the base-case values by ±10%. Additional hypotheses examined involved:

- a licensed (maximum) duration of use for IUD of 5 years (instead of 8 years, as used in the base-case analysis)
- a scenario of combining LARC use with use of male condom
- changes in ingredient and health service costs of the comparators (COC, male condom, female and male sterilisation)

- 'perfect use' of male condom and COC (resulting in substantially lower failure rates).

Finally, a sensitivity analysis by changing the discount rates was undertaken, as recommended by NICE guidance on technology appraisal.[446] Alternative input values and hypotheses tested in sensitivity analyses are reported in the respective sections of the results.

Table 8.3 Effectiveness rates and other clinical input parameters included in the economic model

Input parameter	Baseline value (%)	Comments
Annual failure rate		
IUD		
Year 1	0.5	Annual failure rates were based on 1 year and 8 year cumulative failure rates reported in the guideline. The annual failure rate between 2–8 years was assumed to be stable, as no additional data were available. After reinsertion, the annual failure rate was assumed to be equal to that between 2–8 years, as it was expected to be lower than the failure rate of the first year of first insertion.
Years 2–8:	0.246	
Years 9–15:	0.246	
IUS		
Years 1–5:	0.1	Annual failure rates were based on the 5 year cumulative failure rate reported in the guideline. The annual failure rate between 1–5 years was assumed to be stable, as no additional data were available. After reinsertion, the annual failure rate was assumed to remain the same as in previous years.
Years 6–15:	0.1	
Injectable		
Year 1:	0.1	Annual failure rates were based on cumulative failure rates for the first 2 years of use reported in the guideline. It was assumed that after the second year of use the annual failure rate was stable over time and equal to that of the first year of use.
Year 2:	0.3	
Years 3–15:	0.1	
Implant		
Years 1–15:	0.005	The annual failure rate for the implant was based on GDG expert opinion. All studies included in the guideline reported no pregnancies following use of the implant.
Male condom		
Years 1–15:	15	Failure rate for typical use, based on a published review.[435]
COC		
Years 1–15:	8	Failure rate for typical use, based on a published review.[435]
Female sterilisation		
Year 1:	0.5	The failure rate for the first year was based on a published review.[435] The annual failure rates for the following years are based on the cumulative 10 year rate of the CREST study reported in the RCOG guideline on sterilisation[442] after taking into account the first year's failure rate. The annual failure rate between 2–10 years was assumed to be stable over time, as no additional data were available. For 11 years following sterilisation and above, the annual failure rate was assumed to be the same as that in year 10.
Years 2–10:	0.129	
Years 11–15:	0.129	
Vasectomy		
Year 1:	0.15	The failure rate for the first year was based on a published review.[435] The annual failure rate used for the following years is that reported in the RCOG guideline on sterilisation after clearance has been given.[442]
Years 2–15:	0.05	
Average contraceptive method		
Years 1–15:	12.81	Weighted average failure rate based on contraceptive usage rates in England and Wales for women 'at risk of pregnancy'.[1]
Discontinuation rates		
IUD		
Year 1:	21.6	Discontinuation rates for the first 5 years of IUD use were derived from the mean values of the rates reported in a European multicentre RCT[153] and a UK community-based study, reflecting routine use,[135] both reported in chapter 4. The rates refer to the initial hypothetical cohort of 1000 women starting the method.
Year 2:	13.4	
Year 3:	11.8	
Year 4:	9.05	
Year 5:	5.65	
Following years:	1	The discontinuation rate for following years was based on GDG expert opinion and applied, each year, to the subgroup of women that remained in the cohort in that year, and not to the initial cohort of women.

Table 8.3 Effectiveness rates and other clinical input parameters included in the economic model (continued)

Input parameter	Baseline value (%)	Comments
IUS		
Year 1:	25.25	Discontinuation rates for the first 5 years of IUS use were derived from the mean values of the rates reported in a European multicentre RCT[153] and a UK community-based study, reflecting routine use,[244] both reported in chapter 5. The rates refer to the initial hypothetical cohort of 1000 women.
Year 2:	13.25	
Year 3:	8.4	
Year 4:	5.95	
Year 5:	3.9	The discontinuation rate for following years was based on GDG expert opinion, and applied to the subgroup of women that remained in the cohort each year.
Following years:	1	
Injectable		
Year 1:	50	The discontinuation rate for the first year of injectable use was based on the summary of evidence reported in chapter 6.
Following years:	5	The discontinuation rate for following years was based on GDG expert opinion, and applied to the subgroup of women that remained in the cohort each year.
Implant		
Year 1:	22.5	Discontinuation rates for the first 4 years of implant use (including reinsertion) were derived from the mean values of the rates reported in an international multicentre RCT[53] and a Scottish community-based study, reflecting routine use,[374] both reported in chapter 7. The rates refer to the initial hypothetical cohort of 1000 women.
Year 2:	14.5	
Year 3:	9	
Year 4 (reinsertion):	5	
Following years:	1	The discontinuation rate for following years was based on GDG expert opinion, and applied to the subgroup of women that remained in the cohort each year.
Male condom:	–	It was assumed that no discontinuations occurred in the cohort of women that used male condom for contraception (GDG consensus).
COC		
Year 1:	45	Rates based on GDG expert opinion.
Following years:	10	The discontinuation rate for following years refers to the subgroup of women that remained in the cohort each year.
Female and male sterilisation:	–	For women/couples choosing a non-reversible method (female or male sterilisation) the model assumed that no discontinuations (and subsequent reversals) occurred. In case of contraceptive failure, a repeat of the method was considered (GDG consensus).
Relative probabilities of ectopic pregnancy		
IUD:	6	Based on data reported in the guideline.
IUS:*	6	Based on data reported in the guideline.
Injectable:	1.15	For injectable, implant, male condom, COC, vasectomy and average contraceptive method, the incidence of ectopic pregnancy among pregnancies in the general population in the UK was used.[443]
Implant:	1.15	
Male condom:	1.15	
COC:	1.15	
Female sterilisation:	33	The probability used for female sterilisation was approximately equal to a calculated weighted average probability based on results reported in a cohort study[444] and consistent with the range of values reported in the RCOG guideline on sterilisation[442] and a published review.[445]
Vasectomy:	1.15	For injectable, implant, male condom, COC, vasectomy and average contraceptive method, the incidence of ectopic pregnancy among pregnancies in the general population in the UK was used.[443]
Average contraceptive method:	1.15	
Probabilities of outcomes following unintended pregnancy		
Live birth:	46.4	The probabilities used in the economic analysis account for outcomes resulting from unintended pregnancies. Rates of abortions and live births resulting from all pregnancies (both intended and unintended) are 23.4% and 76.6%, respectively, based on data reported in the National Statistics for England and Wales (stillbirths were considered negligible).[440] No data on the number of conceptions that result in miscarriage are available for England and Wales. Data on miscarriage rates were derived from Scottish Statistics.[441] According to Scottish hospital data, 9% of conceptions result in miscarriage. This percentage was raised to 13% to reflect an additional number of miscarriages (around 30% of all miscarriages) treated in GP practices (GDG expert opinion). After the number of conceptions that led to miscarriage was estimated, the probabilities of outcomes of all conceptions (both intended and unintended) in England and Wales were as follows: abortions 20.3%, live births 66.7%, and miscarriages 13%. Abortions were assumed to derive from unintended pregnancies only, as therapeutic abortions accounted for less than 1% and therefore were considered negligible. The probability of miscarriage is not affected by intention of becoming pregnant, so it is still 13% in the case of unintended pregnancies. It was assumed that 50% of conceptions reported in England and Wales in 2001 were unintended, this assumption being consistent with estimates from other studies.[426,430–432] Consequently, abortions account for 40.6% (20.3% × 2) of unintended pregnancies, which is in agreement with the findings of published studies.[431,433] The remaining 46.4% of unintended pregnancies represents live births.
Miscarriage:	13	
Abortion: (probabilities were assumed to be common to all methods, and were applied to the total number of unintended pregnancies remaining after excluding the cases of ectopic pregnancy)	40.6	
Discount rate:	3.5	Recommended by NICE guidance on technology appraisal,[122] applied both to costs and benefits.

* The economic model results are calculated using the 25% ectopic pregnancy rate for IUS (taken from direct IUS evidence). The GDG later decided that the rate of 6% (taken from IUD) is more realistic. The effects on the results of the economic model are very small.

8.4 Results of the economic analysis

The results of the economic analysis are presented in the form of incremental cost effectiveness ratios (ICERs), expressing 'additional cost per additional pregnancy averted' of one method compared with another. The estimation of this ratio allows for direct comparison between different contraceptive methods, assessing whether the additional benefit (pregnancies averted) is worth the additional cost when switching from one method to another.

$$\text{ICER} = \frac{\text{difference in costs}}{\text{difference in benefits}} \quad \text{between methods}$$

$$= \frac{\text{additional costs associated with use of one method versus another}}{\text{additional pregnancies averted by use of one method versus another}}$$

In the case of one method being both more effective and less costly than its comparator (defined as the 'dominant option'), the calculation of such a ratio is not required. More effective in this context means that the method is associated with a lower number of pregnancies *after discontinuation has been taken into account*, and not simply that the method's clinical effectiveness, dependent on its contraceptive failure rate, is higher that that of the comparator.

Results are presented in two separate sections:

1. comparisons across reversible contraceptive methods (LARC, COC and the male condom)
2. comparison of LARC methods with non-reversible contraceptive methods (female and male sterilisation).

In each section, results of the base-case scenario are presented first, followed by the results of sensitivity analysis. Results of sensitivity analysis are not fully reported unless the alternative assumptions tested have an impact on the relative cost effectiveness of LARC methods.

Conclusions on relative cost effectiveness have been drawn on the basis of dominance of one contraceptive method over its comparator. In the case of one method's being both more effective and more costly than its comparator, then no clear conclusion on relative cost effectiveness could be reached. This would require attaching a monetary value on every unintended pregnancy averted by contraceptive use and, subsequently, determining a cost effectiveness threshold expressing the point above which an additional benefit (unintended pregnancy averted) is not worth the additional cost incurred.

However, the value of averting an unintended pregnancy would be very difficult to determine. The financial cost of an unintended pregnancy (cost saving in the case of preventing such an event) has already been included at the estimation of total costs associated with a contraceptive method; using this cost as a proxy for valuing an unintended pregnancy averted would lead to double counting of respective costs. Moreover, in order to estimate this value, one needs to consider the psychological distress to the woman and her family following an unintended pregnancy, the value of a life foregone due to contraceptive use (or of a life resulting from contraceptive failure), and also the long-term costs and benefits (both financial and intangible) to society associated with an unintended pregnancy (either occurring or averted). Currently, there are no research data to indicate what society is willing to pay in order to prevent an unintended pregnancy. Therefore, although ideally a cost effectiveness threshold should be determined, this was not feasible in the context of this guideline; the lack of establishing an absolute cost effectiveness threshold is acknowledged as a limitation of the analysis.

In some scenarios involving the IUD, the IUS and the implant, results are notably affected by the time frame of the analysis. This is caused to some extent by the time-dependency of the respective method costs: (re)insertion of the above devices is associated with additional healthcare resource use and therefore incurs additional costs in the year in which it occurs. For periods of use ending soon after (re)insertion, average annual costs associated with the above methods are relatively high; these costs decrease as the period of use increases reaching the maximum, licensed duration of use of each LARC device, as high costs of (re)insertion are spread over longer periods of time.

In some cases the ICERs reported are shown to be relatively high. This is explained by the fact that all forms of contraception examined are in general highly effective (this also applies to COC and the male condom when perfect use is achieved); therefore the difference in benefit between methods (the additional number of pregnancies averted) is very small. The difference in associated costs (the additional cost) may also be small (but not *as* small). Therefore, a small additional cost is divided by a *very* small additional number of pregnancies averted, resulting in a relatively large ICER.

Comparison across reversible contraceptive methods: LARC methods, COC, male condom

Base-case analysis

Full base-case results from comparisons across reversible contraceptive methods considered in the analysis are presented in Table 8.4, for all time frames examined, from 1 year to 15 years of contraceptive use. For each time frame all contraceptive methods have been ranked from the most to the least effective. Cases of absolute dominance and extended dominance have been identified and excluded from further analysis (extended dominance of a method occurs where the ICER between this method and the next most effective one following in ranking is higher than the ICER between the preceding most effective method and the method in question). ICERs between the non-dominated methods remaining in the analysis have been subsequently calculated.

Table 8.4 Total costs and pregnancies per 1000 women from 1 to 15 years of contraceptive use

1 year of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	14	262,117	**Implant vs IUD: £17,367/pregnancy averted**
IUS	17	270,749	Dominated by implant
IUD	18	195,442	**IUD vs injectable: £339/pregnancy averted**
Injectable	33	190,534	
COC	91	232,932	Dominated by IUD and injectable
Condom	150	212,658	Dominated by IUD and injectable

2 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	51	322,939	**Implant vs IUD: £17,866/pregnancy averted**
IUD	55	256,572	
IUS	57	337,093	Dominated by implant, IUD
Injectable	99	338,376	Dominated by implant, IUD, IUS
COC	190	406,366	Dominated by all LARC methods
Condom	295	418,125	Dominated by all LARC methods

3 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	101	400,947	**Implant vs IUD: £14,730/pregnancy averted**
IUD	105	337,207	
IUS	109	418,616	Dominated by implant, IUD
Injectable	167	482,178	Dominated by implant, IUD, IUS
COC	289	575,320	Dominated by all LARC methods
Condom	435	616,644	Dominated by all LARC methods

4 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	157	580,444	**Implant vs IUD: £17,163/pregnancy averted**
IUD	166	432,018	
IUS	167	508,869	Dominated by IUD
Injectable	234	622,935	Dominated by implant, IUD, IUS
COC	386	739,765	Dominated by all LARC methods
Condom	570	808,450	Dominated by all LARC methods

Table 8.4 Total costs and pregnancies per 1000 women from 1 to 15 years of contraceptive use (continued)

5 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	215	667,275	Implant vs IUS: £4,598/pregnancy averted	**Implant vs IUD: £7,574/pregnancy averted**
IUS	228	603,534	IUS vs IUD: £18,845/pregnancy averted	Extended dominance
IUD	232	534,555		
Injectable	302	760,600	Dominated by implant, IUD, IUS	
COC	482	899,697	Dominated by all LARC methods	
Condom	701	993,769	Dominated by all LARC methods	

6 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	271	752,269	**Implant vs IUD: £4,052/pregnancy averted**
IUS	290	767,736	Dominated by implant
IUD	299	636,652	
Injectable	370	895,141	Dominated by implant, IUD, IUS
COC	576	1,055,131	Dominated by all LARC methods
Condom	827	1,172,822	Dominated by all LARC methods

7 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	326	909,171	Implant vs IUS: £2,034/pregnancy averted	**Implant vs IUD: £4,424/pregnancy averted**
IUS	351	859,181	IUS vs IUD: £8,459/pregnancy averted	Extended dominance
IUD	365	736,023		
Injectable	437	1,026,537	Dominated by implant, IUD, IUS	
COC	668	1,206,102	Dominated by all LARC methods	
Condom	949	1,345,820	Dominated by all LARC methods	

8 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	380	990,040	Implant vs IUS: £1,413/pregnancy averted	**Implant vs IUD: £3,193/pregnancy averted**
IUS	409	948,186	IUS vs IUD: £5,871/pregnancy averted	Extended dominance
IUD	429	832,635		
Injectable	504	1,154,780	Dominated by implant, IUD, IUS	
COC	758	1,352,655	Dominated by all LARC methods	
Condom	1067	1,512,967	Dominated by all LARC methods	

9 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	432	1,068,882	Implant vs IUS: £989/pregnancy averted	**Implant vs IUD: £1,865/pregnancy averted**
IUS	466	1,034,800	IUS vs IUD: £3,091/pregnancy averted	Extended dominance
IUD	491	958,830		
Injectable	570	1,279,871	Dominated by implant, IUD, IUS	
COC	846	1,494,852	Dominated by all LARC methods	
Condom	1181	1,674,462	Dominated by all LARC methods	

Table 8.4 Total costs and pregnancies per 1000 women from 1 to 15 years of contraceptive use (continued)

10 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	483	1,210,419	Implant vs IUS: £2,339/pregnancy averted	**Implant vs IUD: 2,342/pregnancy averted**
IUS	522	1,119,079	IUS vs IUD: £2,346/pregnancy averted	Extended dominance
IUD	551	1,050,425		
Injectable	635	1,401,818	Dominated by implant, IUD, IUS	
COC	932	1,632,762	Dominated by all LARC methods	
Condom	1291	1,830,496	Dominated by all LARC methods	

11 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	533	1,285,327	Implant vs IUS: £652/pregnancy averted	**Implant vs IUD: £1,892/pregnancy averted**
IUS	576	1,256,971	IUS vs IUD: £3,489/pregnancy averted	Extended dominance
IUD	610	1,139,234		
Injectable	700	1,520,639	Dominated by implant, IUD, IUS	
COC	1016	1,766,460	Dominated by all LARC methods	
Condom	1397	1,981,254	Dominated by all LARC methods	

12 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	588	1,366,633	Implant vs IUS: £451/pregnancy averted	**Implant vs IUD: £1,550/pregnancy averted**
IUS	629	1,336,833	IUS vs IUD: £2,928/pregnancy averted	Extended dominance
IUD	667	1,225,501		
Injectable	764	1,636,357	Dominated by implant, IUD, IUS	
COC	1098	1,896,031	Dominated by all LARC methods	
Condom	1500	2,126,913	Dominated by all LARC methods	

13 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	628	1,486,002	Implant vs IUS: £1,382/pregnancy averted	**Implant vs IUD: £1,883/pregnancy averted**
IUS	680	1,414,530	IUS vs IUD: £2,498/pregnancy averted	Extended dominance
IUD	722	1,309,296		
Injectable	826	1,749,003	Dominated by implant, IUD, IUS	
COC	1177	2,021,563	Dominated by all LARC methods	
Condom	1600	2,267,647	Dominated by all LARC methods	

14 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	674	1,555,286	Implant vs IUS: £1,173/pregnancy averted	**Implant vs IUD: £1,620/pregnancy averted**
IUS	730	1,490,079	IUS vs IUD: £2,159/pregnancy averted	Extended dominance
IUD	776	1,390,690		
Injectable	888	1,858,611	Dominated by implant, IUD, IUS	
COC	1255	2,143,148	Dominated by all LARC methods	
Condom	1695	2,403,622	Dominated by all LARC methods	

Table 8.4 Total costs and pregnancies per 1000 women from 1 to 15 years of contraceptive use (continued)

15 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio	
Implant	719	1,622,769	Implant vs IUS: £999/pregnancy averted	**Implant vs IUD: £1,403/pregnancy averted**
IUS	778	1,563,548	IUS vs IUD: £1,884/pregnancy averted	Extended dominance
IUD	828	1,469,754		
Injectable	948	1,965,220	Dominated by implant, IUD, IUS	
COC	1330	2,260,880	Dominated by all LARC methods	
Condom	1788	2,534,998	Dominated by all LARC methods	

Compared with COC and male condom, LARC methods are associated with a smaller number of unintended pregnancies due to contraceptive failure across all time periods examined. For 1 year of use, COC and the male condom are dominated by two of the LARC methods: the IUD and the injectable. This means that both the IUD and the injectable are not only more effective, but also less costly than male condom and COC over 1 year of use. For longer periods of contraceptive use, COC and male condom are dominated by all LARC methods.

SUMMARY OF EVIDENCE

- LARC methods are more cost effective compared with the COC and the male condom.

The injectable is dominated (is more costly and prevents a lower number of pregnancies) by all other LARC methods, i.e. the IUD, the IUS and the implant, for periods of use starting from 2 and up to 15 years. For 1 year of use, the injectable is the cheapest but also the least effective among LARC methods; the ICER of the IUD (the next most effective method **above** injectable in ranking) versus the injectable for 1 year of use is £339 per pregnancy averted.

The IUS is dominated by the implant for short periods of use, up to 3 years, and also for 6 years of use. In addition, the IUS is dominated by the IUD between 2 and 4 years of use. For the other time frames examined, the IUS is dominated according to the rule of extended dominance: its ICER compared with IUD, which is the next most effective LARC method **below** IUS in ranking, is higher than the ICER between the implant and itself (implant is the next most effective method **above** IUS in ranking).

The implant is the most effective among LARC methods, while the IUD is the least costly among LARC methods. For periods of use up to 4 years, the ICER of implant versus IUD lies within £14,730 (3 years of use) and £17,866 (2 years of use) per pregnancy averted. This ratio falls to £7,574 per pregnancy averted at 5 years of use, and decreases thereafter, reaching a cost of £1,403 per pregnancy averted at 15 years of use, with slight increases at 7, 10 and 13 years of use, due to implant reinsertion costs.

SUMMARY OF EVIDENCE

- The injectable is less cost effective than the IUD, IUS and the implant. Among the latter (IUD, IUS and implant), IUS is the least cost effective.

Results for 1, 3, 5, 8 and 15 years of use are also presented in the form of graphs in Appendix C. The graphs demonstrate the incremental costs and incremental number of unintended pregnancies averted associated with each LARC method compared with COC (results for male condom have not been included in the graphs).

Sensitivity analysis

Varying the failure rates of COC and male condom by ±10%
Varying the failure rates of COC and male condom by ±10% of the base-case values does not affect the base-case results.

Varying the failure rates of LARC methods by ±10%
Varying the failure rates of LARC methods by ±10% of the base-case values does not have any

impact on their cost effectiveness relative to the COC and male condom. In addition, it does not affect ranking of LARC methods in terms of effectiveness, or the cases of dominance (both absolute and extended) across LARC methods. Varying the failure rate of IUD has a moderate impact on the ICERs of the implant versus IUD only for short periods of contraceptive use, up to 3–4 years. ICERs are unaffected when longer periods of use are examined. The range of ICERs between the implant and IUD estimated after changing the failure rates of IUD by ±10% are presented in Appendix D.

SUMMARY OF EVIDENCE

- The cost effectiveness of LARC methods relative to the COC and male condom is robust to modest changes in failure rates. The relative cost effectiveness between LARC methods is also relatively insensitive to modest changes in failure rates, especially in the long run.

Varying the discontinuation rates of LARC methods and COC

Decreasing or increasing discontinuation rates of LARC methods by ±10% of the base-case values does not change their relative cost effectiveness compared with COC and male condom for all time horizons considered. Base-case results are also robust to ±10% changes in the discontinuation rate of COC.

The relative cost effectiveness between LARC methods is substantially affected by altering the LARC discontinuation rates between ±10% of the base-case values. The only exception is the injectable, the relative cost effectiveness of which is insensitive to these changes. The results involving comparisons of injectable with other LARC methods remain unaffected, apart from the two scenarios involving a 10% increase in IUS or a 10% decrease in injectable discontinuation rates, which both result in a delay in the dominance of IUS over the injectable by 1 year, compared with the base-case analysis (this means that under these scenarios dominance starts at 3 years instead of 2 years)

Increasing the base-case discontinuation rates of IUS by 10% of the base-case value results in IUS being constantly dominated by the IUD, across all time horizons examined. Reducing the discontinuation rates of IUS by 10% has a strong impact on the base-case results. The IUS becomes the most effective among LARC methods and dominates the implant starting at 3 years of use and above. The ICERs of IUS versus IUD range between £61 (14 years) and £8,855 (3 years) per pregnancy averted; for 10 and 15 years of use IUS dominates IUD (in addition to its dominance over the implant and the injectable).

Base-case results are also sensitive to a 10% rise in base-case values of discontinuation rates of IUD. The IUS is not dominated by the rule of extended dominance anymore. In fact, it dominates IUD at 10, 14, and 15 years of use. The ICERs of implant versus IUD are lower than those of the respective time frames estimated under the base-case scenario. In contrast, when IUD discontinuation rates are reduced by 10%, IUD dominates IUS for all time horizons examined; it also dominates the implant between 2 and 6 years of use. For the other time horizons, the ICERs of implant versus IUD are, as expected, higher than those of the base-case analysis.

Changes in discontinuation rates of the implant have also a strong impact on the base-case results. A 10% increase in the base-case values leads to implant becoming dominated by IUS for periods of use starting at 4 years and above; IUD also dominates implant for 2–5 years of use. The ICER of implant versus IUD for 1 year of use rises to £29,134 per pregnancy averted. A 10% reduction in the discontinuation rates of implant substantially reduces its ICERs versus IUD compared with the base-case analysis. Under this scenario, IUS is, as in the base-case analysis, constantly dominated either by implant and/or IUD, or by the rule of extended dominance.

The results from comparisons between IUS, IUD and the implant under all scenarios involving changes in their discontinuation rates are provided in Appendix D.

SUMMARY OF EVIDENCE

- The relative cost effectiveness of LARC methods compared with COC and male condom is not sensitive to modest changes in discontinuation rates.

- Discontinuation is an important driver of relative cost effectiveness between LARC methods, with the exception of the injectable; changes in discontinuation rates of LARC methods by 10% of the base-case values affect significantly the relative cost effectiveness between IUS, IUD and the implant.

Applying a 5 year licensed duration of use for IUD

This scenario was considered as some IUDs are only licensed for 5 years of use, and therefore removal of the device and reinsertion needs to take place at the end of 5 and 10 years when longer time frames are examined, and not only at the end of 8 years, as happens with the 8 year licensed IUD used in the base-case analysis. A sensitivity analysis investigated whether this difference in resource use and associated costs had any impact on the cost effectiveness of IUD compared with other contraceptive methods.

The results are not sensitive to such a hypothesis. The ICERs of implant versus IUD are only slightly affected (between 6 and 15 years of use). A shorter licensed duration of use has no impact on relative cost effectiveness between IUD and the other contraceptive methods assessed.

SUMMARY OF EVIDENCE

- The cost effectiveness of IUD is similar for both a 5 and an 8 year licensed duration of use.

LARC methods combined with male condom versus male condom alone

A sensitivity analysis was undertaken to compare the combination of LARC methods and male condom versus male condom alone. This was considered appropriate, as many condom users are likely to be at high-risk for STIs, and therefore select this method not only for purposes of contraception, but also for protection against STIs. Consequently, a meaningful comparison should incorporate this parameter (protection against STIs) in both interventions assessed.

Failure rates of the combination of each LARC method with male condom were assumed to be those of the LARC method alone (additional contraceptive protection of male condom was thought to be negligible), and, as a result, failure costs (associated with outcomes of unintended pregnancy) were also equal to those related to the LARC method alone. Method costs of the combination were the sum of LARC method costs plus the male condom method costs. Discontinuation rates were assumed to be equal to those of LARC methods alone.

The results were only slightly sensitive to this scenario. For 1 year of contraceptive use, the injectable/male condom dominates the male condom alone. For periods of use from 2 years to 15 years, all LARC method combinations with male condom dominate the male condom alone.

SUMMARY OF EVIDENCE

- LARC methods combined with male condom are more cost effective than the male condom alone.

Varying the method costs of COC

Using the lowest ingredient cost for COC,[122] assuming a shorter follow-up consultation time of 5 minutes (instead of 10 minutes) every 6 months for COC or one (instead of two) follow-up consultation of 10 minutes annually, or combining scenarios for ingredient cost and consultation times, does not have any strong impact on the results; the cases of dominance remain the same as those of the base-case scenario.

SUMMARY OF EVIDENCE

- The relative cost effectiveness between LARC and COC is not affected by changes in ingredient cost and/or the duration and frequency of follow-up consultations of COC.

Varying the method costs of male condom

The annual use of 52 condoms at a cost of 56p each, used in the base-case scenario, is a rather conservative assumption. A sensitivity analysis using a price per item of 19p (a price at which primary care practices are likely to buy condoms in bulk, as suggested by the GDG) does not change the results substantially, in either the base-case scenario or the alternative scenario of

LARC methods combined with male condom. For 1 year of use, the IUD becomes only slightly more costly than male condom, while the injectable remains dominant; similarly, the combination of injectable/male condom becomes slightly more costly than male condom alone, for 1 year of use. All LARC methods (alone or combined with male condom) become dominant after 1 year of use, compared with male condom. Increasing the number of condoms used per year or the ingredient cost of condoms would only favour LARC methods further.

SUMMARY OF EVIDENCE

- The relative cost effectiveness between LARC methods and male condom is not sensitive to changes in the ingredient cost of male condom or the number of items used annually.

Perfect use of male condom

Under this scenario perfect use of male condom was assumed, characterised by an annual failure rate equal to 2%, as reported in a published review.[435] Male condom dominates all LARC methods, used alone or in combination with male condom, after 1 year of use. Its dominance over the injectable starts at 1 year of use. The other LARC methods, combined with male condom or alone, are slightly more effective than perfect use of male condom at 1 year of use, but at a substantially higher cost.

These results are explained by the high discontinuation rates of LARC methods, which lead to use of the average contraceptive method, which is far less effective than perfect use of male condom (failure rates of 12.84% versus 2%, respectively). In contrast, no discontinuation was assumed with respect to the male condom. Results for 1 year to 4 years of use are shown in Appendix D.

SUMMARY OF EVIDENCE

- The male condom is more cost effective than LARC methods (used alone or in combination with male condom) when perfect use of it is achieved, owing to high discontinuation rates characterising LARC methods.

Perfect use of COC

Perfect use of COC is characterised by an annual failure rate equal to 0.3%, as reported in a published review.[435] Results remain relatively robust regarding IUD and IUS when perfect use of COC is assumed. IUD dominates COC for time frames of 2 years or more, while the dominance of IUS over COC starts at 4 years of use. The implant remains more effective, but it is also more costly for short periods of use (up to 5 years), with the exception of 3 years of use, where implant is the dominant option. For periods of use of 6 years and above, the implant dominates COC. When COC is perfectly used, it dominates the injectable for periods of use up to 6 years. After this time, the injectable becomes more effective for the rest of the time horizons examined, but at additional cost.

The above results are not as favourable for perfect use of COC as for perfect use of male condom. This is explained by the high discontinuation rates characterising the use of COC, which reduce its overall effectiveness despite perfect use (for male condom no discontinuation was assumed). Full results of this scenario are also presented in Appendix D.

SUMMARY OF EVIDENCE

- The relative cost effectiveness of LARC methods compared with COC is reduced when perfect use of COC is achieved. Nevertheless, IUD, IUS and the implant become more cost effective than perfect use of COC with increasing durations of use. Perfect use of COC is more cost effective than the injectable for periods of contraceptive use of up to 6 years.

Varying the discount rate between 0% and 6%

This scenario was investigated as recommended by NICE guidance on technology appraisal.[446] None of the base-case results is sensitive to changes in discount rate.

Comparison of LARC methods with non-reversible contraceptive methods (female and male sterilisation)

Base-case analysis

As shown in Table 8.5, both female and male sterilisation dominate all LARC methods at 15 years of contraceptive protection. This is explained by the high discontinuation rates of LARC that lead to the use of less effective contraceptive methods (captured in the concept of average contraceptive method, as described earlier).

Table 8.5 Comparison of LARC with male and female sterilisation

15 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Male sterilisation	7	466,776	
Female sterilisation	19	750,191	
Implant	719	1,622,769	Dominated by male and female sterilisation
IUS	778	1,563,548	Dominated by male and female sterilisation
IUD	828	1,469,754	Dominated by male and female sterilisation
Injectable	948	1,965,220	Dominated by male and female sterilisation

SUMMARY OF EVIDENCE

- Female and male sterilisation are more cost effective than LARC methods at 15 years of contraceptive use.

Results for female and male sterilisation are included in the graph provided in Appendix C, for 15 years of contraceptive use. As with the results for LARC methods, incremental costs and benefits associated with sterilisation have been calculated using the COC as the baseline comparator, in order to illustrate the differences in relative cost effectiveness between all methods considered in the economic analysis (COC, LARC, female and male sterilisation) in a single graph.

Sensitivity analysis

Varying the failure rates of female and male sterilisation by ±10%
Varying the failure rates of female and male sterilisation by ±10% of the base-case values does not have any impact on the results of the analysis.

Varying the failure rates of LARC methods by ±10%
The cost effectiveness of LARC methods compared with non-reversible contraceptive methods is not affected by varying LARC failure rates by ±10% of their base-case values.

SUMMARY OF EVIDENCE

- The relative cost effectiveness of LARC methods compared with female and male sterilisation is robust to modest changes in either LARC or sterilisation failure rates.

Varying the discontinuation rates of LARC methods by ±10%
The cost effectiveness of LARC compared with male and female sterilisation is not affected by modest changes in LARC discontinuation rates.

SUMMARY OF EVIDENCE

- The cost effectiveness of LARC methods compared with male and female sterilisation is not sensitive to modest changes in LARC discontinuation rates.

Varying the sterilisation procedure costs by ±20%
Base-case results are not affected by a 20% increase or decrease in female and male sterilisation costs.

SUMMARY OF EVIDENCE

- The relative cost effectiveness between LARC methods and sterilisation (female and male) is not affected by 20% changes in sterilisation costs.

Varying the discount rate between 0% and 6%

Base-case results from comparisons of LARC methods with female and male sterilisation are insensitive to changes in discount rate.

8.5 Limitations of the economic analysis – further considerations

The economic analysis was based on best available evidence. The validity of the results is higher when shorter time frames are considered, as in this case effectiveness and discontinuation rates were mainly based on available data reported in the guideline and not on further assumptions. In some cases, results on relative cost effectiveness of LARC methods were found to be highly sensitive to changes in discontinuation rates; owing to high uncertainty characterising this input parameter, a rigorous interpretation of the results followed by relevant recommendations was allowed only where results were clearly shown not to be driven by discontinuation rates.

The decision-analytic model incorporated events such as contraceptive failure leading to unintended pregnancy, and discontinuation. The latter was demonstrated to be a significant determinant of the relative cost effectiveness between LARC methods. However, other events associated with contraceptive use were not reflected in the results. Use of LARC methods is often followed by side effects. Besides causing distress to the user, some side effects may require additional healthcare resource use for their management (e.g. hospitalisation), which has not been considered in the model; this is acknowledged as a limitation of the analysis. Nevertheless, the frequency of side effects related to LARC use is partially reflected in rates of discontinuation (since a proportion of discontinuations is due to side effects), and the possibility and consequences of such an event (subsequent use of a less effective method and increased risk of contraceptive failure) was included in the model design.

In addition, other non-contraceptive benefits, such as the management of menstrual disorders achieved with IUS use and the protective role of male condom against STIs, were not considered in the analysis. In the case of IUS, including such a beneficial effect might substantially improve the method's relative cost effectiveness compared with other LARC methods. Regarding the omission of the protective role of male condom against STIs from the model structure, a sensitivity analysis evaluated the cost effectiveness of LARC methods combined with male condom versus male condom alone. In this case, both comparators provided protection against STIs, and the limitation of not taking into account this non-contraceptive benefit associated with use of condom was overcome. This sensitivity analysis showed that LARC methods used in combination with the male condom were more cost effective than the male condom.

Psychological factors, such as the satisfaction and quality of life arising from contraceptive use, or the distress to the woman and her family following an unintended pregnancy, the value of a life foregone due to contraceptive use or a life resulting from a contraceptive failure, were also not taken into account in the economic analysis.

The analysis included comparison of LARC methods with non-reversible contraception (female and male sterilisation). However, the latter cannot always be considered as an alternative to LARC use. Comparison of LARC methods with male sterilisation presupposes the couple as the 'unit of protection' and not the woman alone. Female sterilisation is not a realistic option for women who wish to retain their fertility. Furthermore, it has been reported that 10% of couples that have chosen sterilisation as their method of contraception regret this decision at a later date, while only 1% of them undergo a reversal procedure.[449] In all these cases, use of LARC methods can be regarded as a relevant contraceptive option.

Users' compliance is an important issue that has to be taken into account in the interpretation of the results. Perfect use of COC (which has been demonstrated to be more cost effective than some LARC methods for various durations of use) requires perfect compliance with the method. This is not the case in particular for certain subgroups of the population, such as adolescents[450]

or women with no established regular routine.[451] The use of LARC methods in such cases is more cost effective, since their effectiveness in practice does not depend on users' compliance.

In conclusion, cost effectiveness of LARC methods is only one factor to consider when making choices about contraception. At an individual level, women's preferences, individual needs, lifestyle and the acceptability of the method should determine the final decision on which contraceptive method to use.

RECOMMENDATION

C

Contraceptive service providers should be aware that

- all currently available LARC methods (intrauterine devices [IUDs], the intrauterine system [IUS], injectable contraceptives and implants) are more cost effective than the combined oral contraceptive pill even at 1 year of use
- IUDs, the IUS and implants are more cost effective than the injectable contraceptives
- increasing the uptake of LARC methods will reduce the number of unintended pregnancies.

9. Auditable standards

Table 9.1 Suggested audit criteria

Recommendation	Criterion	Exceptions	Definitions of terms
Women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception (LARC) methods	Percentage of women requiring contraception who have it documented in their notes that they have been informed and offered a choice of all contraceptive methods, including LARC methods	Women requiring short-term contraception	
Women considering LARC methods should receive detailed information – both verbal and written – that will enable them to choose a method and use it effectively. This information should take into consideration their individual needs and should include: • contraceptive efficacy • duration of use • risks and possible side effects • non-contraceptive benefits • the procedure for initiation and • removal/discontinuation • when to seek help while using the method	Percentage of women considering LARC methods who have it documented in their notes that they have received information that enables them to choose and use the method effectively	None	
Healthcare professionals advising women about contraceptive choices should be competent to: • help women to consider and compare the risks and benefits of all methods relevant to their individual needs • manage common side effects and problems	Percentage of healthcare professionals advising women about contraceptive choices who receive training and are competent to: • assist women to consider and compare the risks and benefits of all methods relevant to their individual needs • manage common side effects and problems	None	Guidance for training for doctors and nurses can be obtained from the FFPRHC (Faculty of Family Planning and Reproductive Health Care) and the RCN (Royal College of Nursing)
Contraceptive service providers who do not provide LARC in their practice or service should have an agreed mechanism in place for referring women for LARC	Percentage of documented LARC referrals by healthcare professionals who do not provide LARC within their own practice/service Percentage of practices/services with written protocol for referral for LARC if not provided in-house	None	
Healthcare professionals providing intrauterine or subdermal contraceptives should receive training to develop and maintain the relevant skills to provide these methods	Percentage of healthcare professionals providing intrauterine or subdermal contraceptives who have received training to develop relevant skills to provide these methods, and evidence of ongoing CPD (continuing professional development) and practice	None	Guidance for training for doctors and nurses can be obtained from the FFPRHC (Faculty of Family Planning and Reproductive Health Care) and the RCN (Royal College of Nursing)
Contraceptive service providers should be aware that: • all currently available LARC methods (intrauterine devices [IUDs], the intrauterine system [IUS], injectable contraceptives and implants) are more cost effective than the combined oral contraceptive pill even at 1 year of use • IUDs, the IUS and implants are more cost effective than the injectable contraceptives • increasing the uptake of LARC methods will reduce the numbers of unintended pregnancies	Contraceptive service providers should audit the uptake of LARC	None	

Appendix A

Summary of changes after stakeholders consultation

A.1 Main issues raised

The main issues raised during the second stakeholder consultation and the Institute's validation processes were:

- clarifying the health economics analyses for integration into the guideline
- clarifying the advice to healthcare professionals and women with regard to testing for sexually transmitted diseases
- improving the presentation of the documents.

A.2 Major changes

The guideline developers have carefully considered all of the second consultation and validation comments. The main changes to the final document since the second consultation are summarised below.

Key recommendation added

Contraceptive service providers should be aware that:

- all currently available LARC methods (IUDs, IUS, injectable contraceptives and implants) are more cost effective than the combined oral contraceptive pill even at 1 year of use
- the IUDs, the IUS and implants are more cost effective than the injectable contraceptives
- increasing the uptake of LARC methods will reduce the number of unintended pregnancies.

Recommendations clarified: testing for sexually transmitted infections

Testing for the following infections should be undertaken before IUD insertion:

- *Chlamydia trachomatis* in women at risk of STIs
- *Neisseria gonorrhoeae* in women from areas where the disease is prevalent and who are at risk of STIs
- any STIs in women who request it.

Testing for the following infections should be undertaken before IUS insertion:

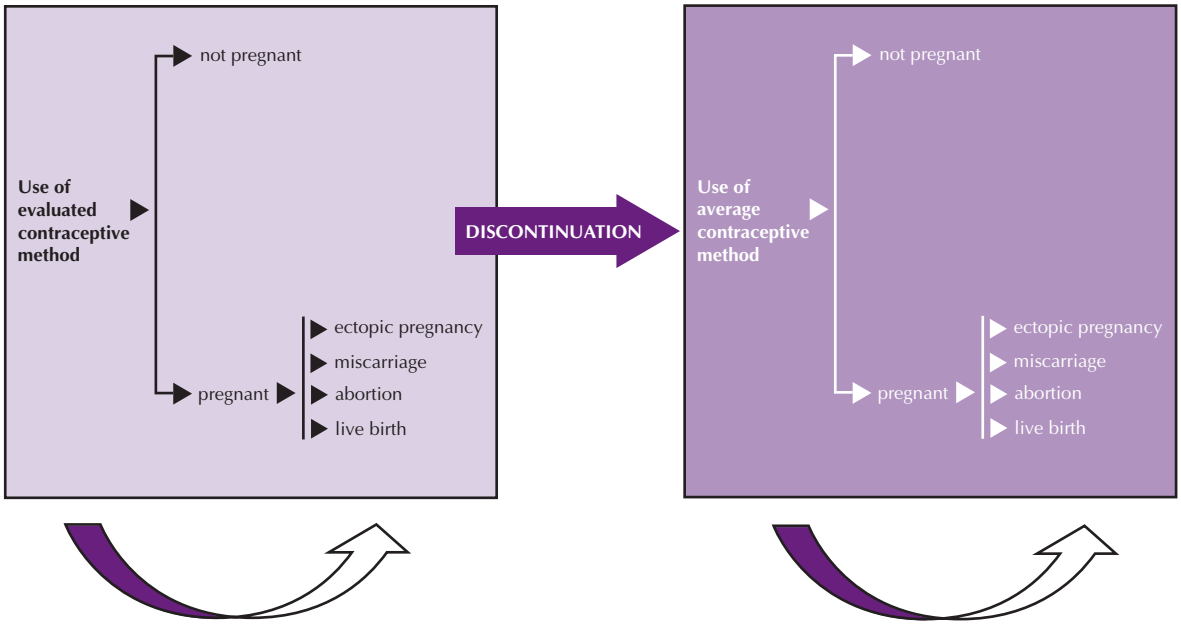
- *Chlamydia trachomatis* in women at risk of STIs
- *Neisseria gonorrhoeae* in women from areas where the disease is prevalent and who are at risk of STIs
- any STIs in women who request it.

Guideline presentation

The NCC-WCH, NICE and the Family Planning Association have revised/improved the format and presentation of the final guideline and associated documents.

Appendix B

Schematic structure of the decision-analytic model used in the economic analysis

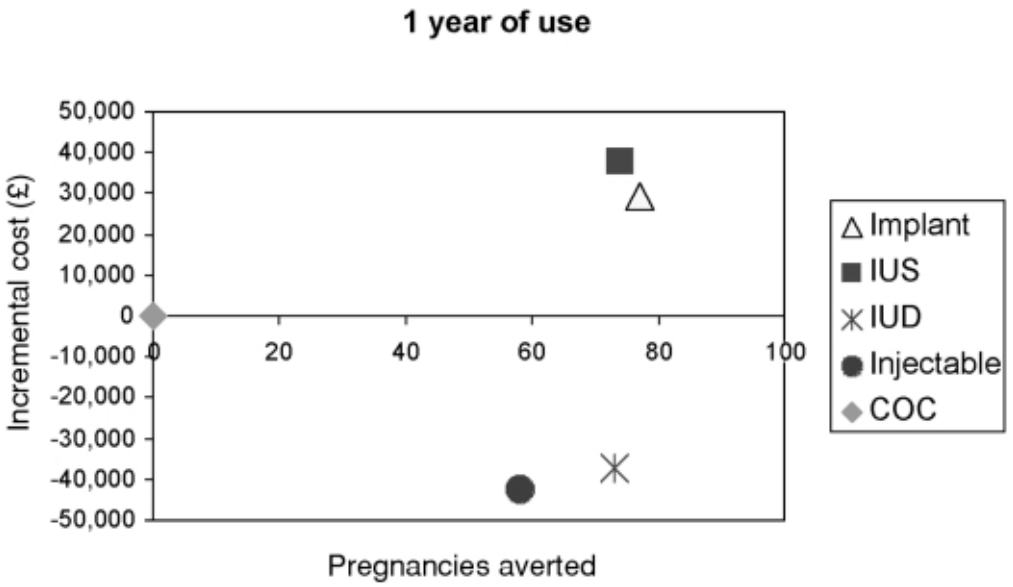


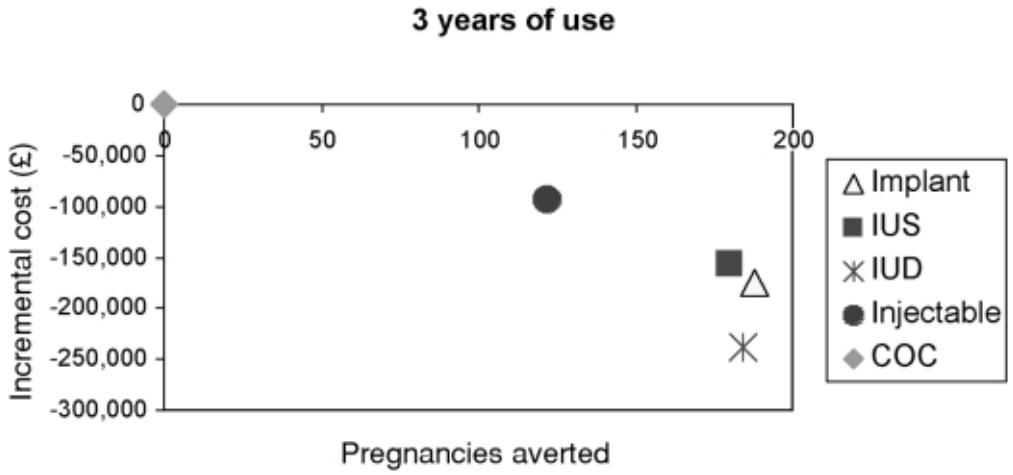
The diagram shows the two states of the decision model: the state of using one of the contraceptive methods evaluated in the economic analysis, and the following state of using the average contraceptive method; while being in any of these states, a woman under contraceptive protection may not become pregnant, or she may experience an unintended pregnancy due to contraceptive failure (with all the associated outcomes). All women in the hypothetical cohort enter the state of using one of the contraceptive methods evaluated; from this state, a woman may discontinue and move to the state of the average contraceptive method, or she may remain on the method evaluated; once having moved to the state of the average contraceptive method, the woman remains on it for the rest of the time frame examined.

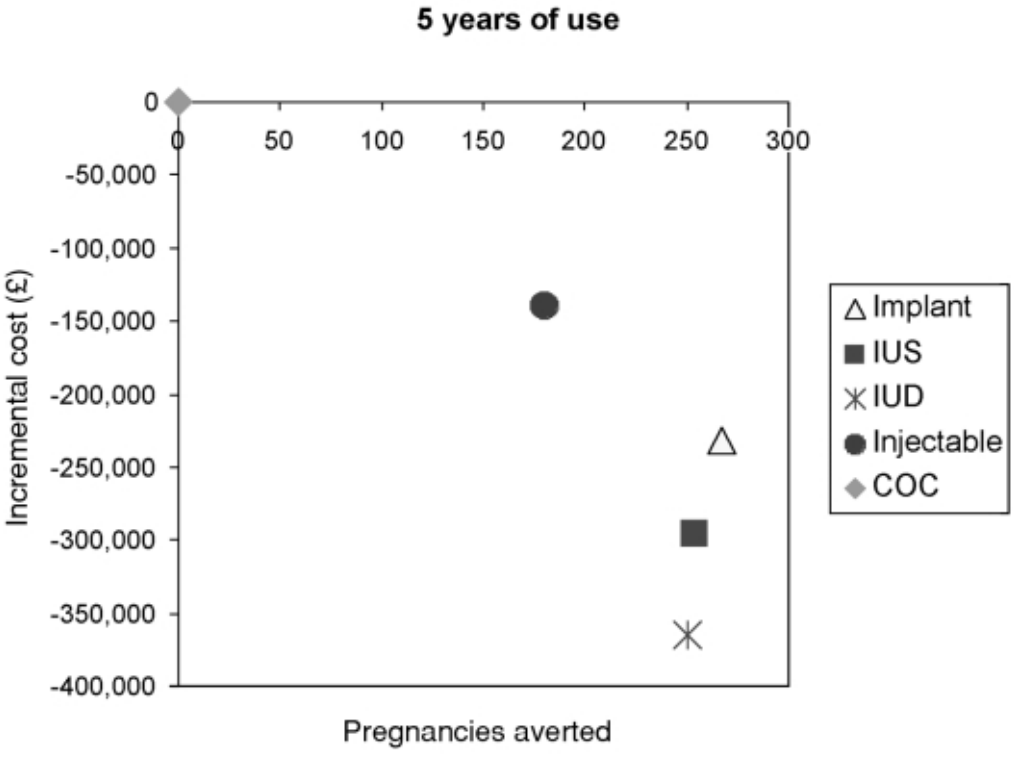
Appendix C

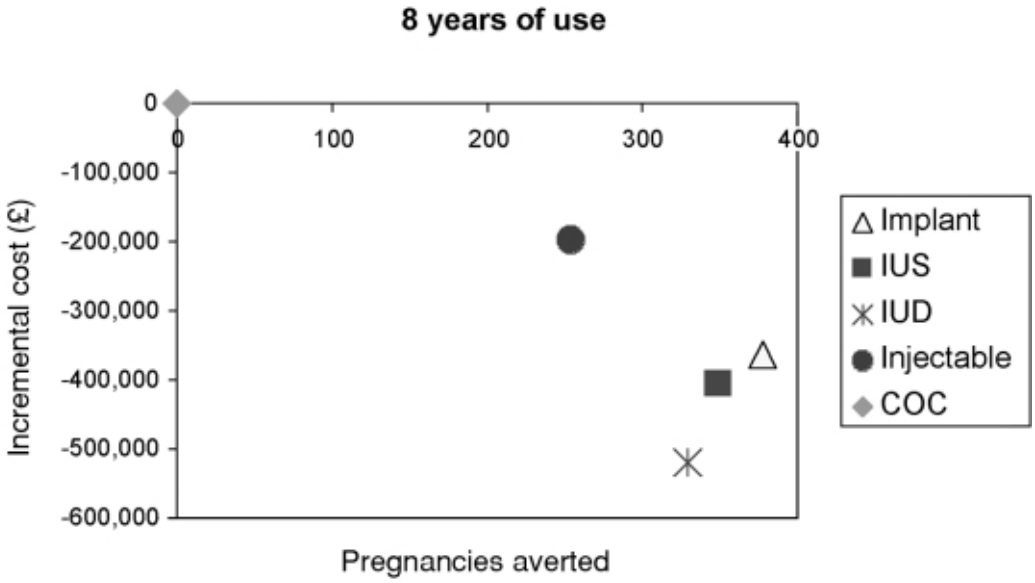
Results of cost effectiveness analysis in the form of graphs

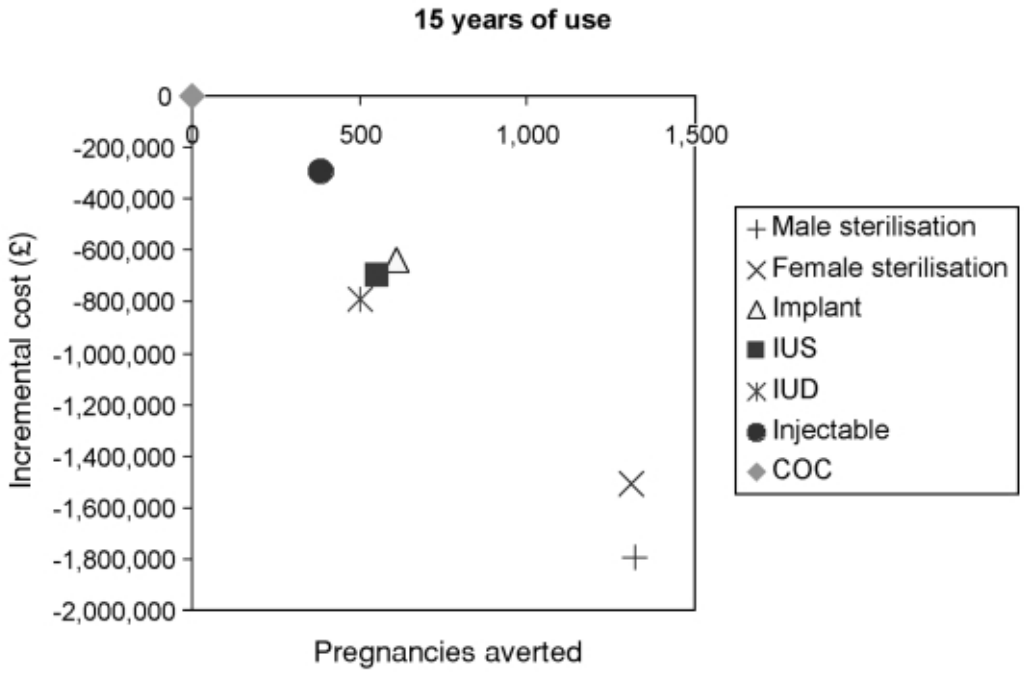
The graphs below demonstrate the incremental costs and incremental number of unintended pregnancies averted associated with switching from use of COC to use of a LARC method. Results refer to a hypothetical cohort of 1000 women. Negative incremental costs reflect net cost savings gained by using a LARC method instead of COC. The graph for 15 years time horizon provides also incremental costs and incremental number of unintended pregnancies averted associated with female and male sterilisation versus use of COC.




3 years of use
Incremental cost (£)
0
-50,000
-100,000
-150,000
-200,000
-250,000
-300,000
0
50
100
150
200
Pregnancies averted
Implant
IUS
IUD
Injectable
COC


5 years of use
Incremental cost (£)
0
-50,000
-100,000
-150,000
-200,000
-250,000
-300,000
-350,000
-400,000
0
50
100
150
200
250
300
Pregnancies averted
Implant
IUS
IUD
Injectable
COC


8 years of use
0
0
100
200
300
400
-100,000
-200,000
-300,000
-400,000
-500,000
-600,000
Incremental cost (£)
Pregnancies averted
Implant
IUS
IUD
Injectable
COC


15 years of use
0
0
500
1,000
1,500
-200,000
-400,000
-600,000
-800,000
-1,000,000
-1,200,000
-1,400,000
-1,600,000
-1,800,000
-2,000,000
Incremental cost (£)
Pregnancies averted
Male sterilisation
Female sterilisation
Implant
IUS
IUD
Injectable
COC

Appendix D

Results of the sensitivity analysis

D.1 Varying failure rates of IUD by ±10%

The table shows the ranges of ICERs between the implant and the IUD resulting from changing the base-case value of the IUD failure rate by ±10%.

Duration of use	ICERs following changes of +10% and –10% in IUD failure rates
1 year	£15,430 – £19,813
2 years	£15,132 – £21,688
3 years	£12,348 – £18,115
4 years	£15,487 – £19,210
5 years	£7,115 – £8,087
6 years	£3,863 – £4,254
7 years	£4,265 – £4,592
8 years	£3,086 – £3,304
9 years	£1,799 – £1,933
10 years	£2,273 – £2,414
11 years	£1,836 – £1,951
12 years	£1,502 – £1,599
13 years	£1,832 – £1,935
14 years	£1,575 – £1,666
15 years	£1,363 – £1,444

D.2 Varying LARC discontinuation rates – comparisons across IUS, IUD and implant

(a) Increasing IUS discontinuation rates by 10%

Duration of use	LARC method	Total pregnancies	Total costs (£)
1 year	IUD	18	195,442
	IUS	19	274,397
2 years	IUD	57	337,093
	IUS	63	347,316
3 years	IUD	105	337,207
	IUS	119	436,935
4 years	IUD	166	432,018
	IUS	183	536,158
5 years	IUD	232	534,555
	IUS	251	640,237
6 years	IUD	299	636,652
	IUS	319	804,427
7 years	IUD	365	736,023
	IUS	385	904,801
8 years	IUD	429	832,635
	IUS	449	1,002,406
9 years	IUD	491	958,830
	IUS	512	1,097,299
10 years	IUD	551	1,050,425
	IUS	573	1,189,547
11 years	IUD	610	1,139,234
	IUS	632	1,327,438
12 years	IUD	667	1,225,501
	IUS	689	1,414,683
13 years	IUD	722	1,309,296
	IUS	745	1,499,483
14 years	IUD	776	1,390,690
	IUS	799	1,581,869
15 years	IUD	828	1,469,754
	IUS	852	1,661,917

As shown in the table, IUD dominates IUS (i.e. it is more effective and less costly) across all time periods examined.

(b) Decreasing IUS discontinuation rates by 10%

Duration of use	LARC method	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
1 year	Implant	14	262,117	**Implant vs IUD: £17,367/pregnancy averted**
	IUS	15	267,102	Dominated by implant
	IUD	18	195,442	
2 years	Implant	51	322,939	**Implant vs IUD: £17,866/pregnancy averted**
	IUS	52	326,870	Dominated by implant
	IUD	55	256,572	
3 years	IUS	98	400,297	**IUS vs IUD: £8,855/pregnancy averted**
	Implant	101	400,947	Dominated by IUS
	IUD	105	337,207	
4 years	IUS	151	481,579	**IUS vs IUD: £3,272/pregnancy averted**
	Implant	157	580,444	Dominated by IUS
	IUD	166	432,018	
5 years	IUS	206	566,831	**IUS vs IUD: £1,240/pregnancy averted**
	Implant	215	667,275	Dominated by IUS
	IUD	232	534,555	
6 years	IUS	262	731,034	**IUS vs IUD: £2,506/pregnancy averted**
	Implant	271	752,269	Dominated by IUS
	IUD	299	636,652	
7 years	IUS	316	813,522	**IUS vs IUD: £1,585/pregnancy averted**
	Implant	326	909,171	Dominated by IUS
	IUD	365	736,023	
8 years	IUS	369	893,885	**IUS vs IUD: £1,026/pregnancy averted**
	Implant	380	990,040	Dominated by IUS
	IUD	429	832,635	
9 years	IUS	421	972,161	**IUS vs IUD: £190/pregnancy averted**
	Implant	432	1,068,882	Dominated by IUS
	IUD	491	958,830	
10 years	IUS	471	1,048,398	
	Implant	483	1,210,419	Dominated by IUS
	IUD	551	1,050,425	Dominated by IUS
11 years	IUS	520	1,186,280	**IUS vs IUD: £525/pregnancy averted**
	Implant	533	1,285,327	Dominated by IUS
	IUD	610	1,139,234	
12 years	IUS	568	1,258,664	**IUS vs IUD: £336/pregnancy averted**
	Implant	588	1,366,633	Dominated by IUS
	IUD	667	1,225,501	
13 years	IUS	614	1,329,150	**IUS vs IUD: £184/pregnancy averted**
	Implant	628	1,486,002	Dominated by IUS
	IUD	722	1,309,296	
14 years	IUS	660	1,397,745	**IUS vs IUD: £61/pregnancy averted**
	Implant	674	1,555,286	Dominated by IUS
	IUD	776	1,390,690	
15 years	IUS	704	1,464,509	
	Implant	719	1,622,769	Dominated by IUS
	IUD	828	1,469,754	Dominated by IUS

(c) Increasing IUD discontinuation rates by 10%

Duration of use	LARC method	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
1 year	Implant	14	262,117	**Implant vs IUD: £12,315/pregnancy averted**
	IUS	17	270,749	Dominated by implant
	IUD	20	198,463	
2 years	Implant	51	322,939	**Implant vs IUD: £6,783/pregnancy averted**
	IUS	57	337,093	Dominated by implant
	IUD	60	265,419	
3 years	Implant	101	400,947	**Implant vs IUD: £3,389/pregnancy averted**
	IUS	109	418,616	Dominated by implant
	IUD	115	353,879	
4 years	Implant	157	580,444	**Implant vs IUS: £7,300/pregnancy averted**
	IUS	167	508,869	**IUS vs IUD: £3,581/pregnancy averted**
	IUD	181	457,940	
5 years	Implant	215	667,275	**Implant vs IUS: £4,598/pregnancy averted**
	IUS	228	603,534	**IUS vs IUD: £1,297/pregnancy averted**
	IUD	254	570,509	
6 years	Implant	271	752,269	**Implant vs IUDD: £1,227/pregnancy averted**
	IUS	290	767,736	Dominated by implant
	IUD	328	682,539	
7 years	Implant	326	909,171	**Implant vs IUS: £2,034/pregnancy averted**
	IUS	351	859,181	**IUS vs IUD: £1,377/pregnancy averted**
	IUD	400	791,487	
8 years	Implant	380	990,040	**Implant vs IUS: £1,413/pregnancy averted**
	IUS	409	948,186	**IUS vs IUD: £843/pregnancy averted**
	IUD	470	897,315	
9 years	Implant	432	1,068,882	**Implant vs IUS: £989/pregnancy averted**
	IUS	466	1,034,800	**IUS vs IUD: £110/pregnancy averted**
	IUD	537	1,026,984	
10 years	Implant	483	1,210,419	**Implant vs IUS: £2,339/pregnancy averted**
	IUS	522	1,119,079	
	IUD	603	1,127,088	Dominated by IUS
11 years	Implant	533	1,285,327	**Implant vs IUS: £652/pregnancy averted**
	IUS	576	1,256,971	**IUS vs IUD: £361/pregnancy averted**
	IUD	667	1,224,080	
12 years	Implant	588	1,366,633	**Implant vs IUS: £451/pregnancy averted**
	IUS	629	1,336,833	**IUS vs IUD: £185/pregnancy averted**
	IUD	729	1,318,210	
13 years	Implant	628	1,486,002	**Implant vs IUS: £1,382/pregnancy averted**
	IUS	680	1,414,530	**IUS vs IUD: £45/pregnancy averted**
	IUD	790	1,409,564	
14 years	Implant	674	1,555,286	**Implant vs IUS: £1,173/pregnancy averted**
	IUS	730	1,490,079	
	IUD	848	1,498,222	Dominated by IUS
15 years	Implant	719	1,622,769	**Implant vs IUS: £999/pregnancy averted**
	IUS	778	1,563,548	
	IUD	905	1,584,269	Dominated by IUS

(d) Decreasing IUD discontinuation rates by 10%

Duration of use	LARC method	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
1 year	Implant	14	262,117	**Implant vs IUD: £27,771/pregnancy averted**
	IUD	17	192,420	
	IUS	17	270,749	Dominated by implant, IUD
2 years	IUD	50	247,725	
	Implant	51	322,939	Dominated by IUD
	IUS	55	256,572	Dominated by IUD
3 years	IUD	96	320,535	
	Implant	101	400,947	Dominated by IUD
	IUS	109	418,616	Dominated by IUD, implant
4 years	IUD	150	406,095	
	Implant	157	580,444	Dominated by IUD
	IUS	167	508,869	Dominated by IUD, implant
5 years	IUD	210	498,602	
	Implant	215	667,275	Dominated by IUD
	IUS	228	603,534	Dominated by IUD
6 years	IUD	271	590,755	
	Implant	271	752,269	Dominated by IUD
	IUS	290	767,736	Dominated by IUD, implant
7 years	Implant	326	909,171	**Implant vs IUD: £50,467/pregnancy averted**
	IUD	330	680,520	
	IUS	351	859,181	Dominated by IUD
8 years	Implant	380	990,040	**Implant vs IUD: £25,759/pregnancy averted**
	IUD	388	767,873	
	IUS	409	948,186	Dominated by IUD
9 years	Implant	432	1,068,882	**Implant vs IUD: £14,268/pregnancy averted**
	IUD	444	890,562	
	IUS	466	1,034,800	Dominated by IUD
10 years	Implant	483	1,210,419	**Implant vs IUD: 14,657/pregnancy averted**
	IUD	499	973,571	
	IUS	522	1,119,079	Dominated by IUD
11 years	Implant	533	1,285,327	**Implant vs IUD: £11,783/pregnancy averted**
	IUD	552	1,054,109	
	IUS	576	1,256,971	Dominated by IUD
12 years	Implant	588	1,366,633	**Implant vs IUD: £9,867/pregnancy averted**
	IUD	604	1,132,410	
	IUS	629	1,336,833	Dominated by IUD
13 years	Implant	628	1,486,002	**Implant vs IUD: £10,676/pregnancy averted**
	IUD	654	1,208,533	
	IUS	680	1,414,530	Dominated by IUD
14 years	Implant	674	1,555,286	**Implant vs IUD: £9,432/pregnancy averted**
	IUD	703	1,282,539	
	IUS	730	1,490,079	Dominated by IUD
15 years	Implant	719	1,622,769	**Implant vs IUD: £8,469/pregnancy averted**
	IUD	750	1,354,488	
	IUS	778	1,563,548	Dominated by IUD

(e) Increasing implant discontinuation rates by 10%

Duration of use	LARC method	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
1 year	Implant	16	265,323	**Implant vs IUD: £29,134/pregnancy averted**
	IUS	17	270,749	Dominated by implant
	IUD	18	195,442	
2 years	IUD	55	256,572	
	Implant	56	332,406	Dominated by IUD
	IUS	57	337,093	Dominated by implant
3 years	IUD	105	337,207	
	IUS	109	418,616	Dominated by IUD
	Implant	111	418,387	Dominated by IUD
4 years	IUD	166	432,018	
	IUS	167	508,869	Dominated by IUD
	Implant	173	598,715	Dominated by IUS, IUD
5 years	IUS	228	603,534	**IUS vs IUD: £18,845/pregnancy averted**
	IUD	232	534,555	
	Implant	236	694,390	Dominated by IUS, IUD
6 years	IUS	290	767,736	**IUS vs IUD: £14,226/pregnancy averted**
	Implant	298	787,977	Dominated by IUS
	IUD	299	636,652	
7 years	IUS	351	859,181	**IUS vs IUD: £8,459/pregnancy averted**
	Implant	358	945,064	Dominated by IUS
	IUD	365	736,023	
8 years	IUS	409	948,186	**IUS vs IUD: £5,871/pregnancy averted**
	Implant	417	1,033,935	Dominated by IUS
	IUD	429	832,635	
9 years	IUS	466	1,034,800	**IUS vs IUD: £3,091/pregnancy averted**
	Implant	475	1,120,494	Dominated by IUS
	IUD	491	958,830	
10 years	IUS	522	1,119,079	**IUS vs IUD: £2,346/pregnancy averted**
	Implant	530	1,262,195	Dominated by IUS
	IUD	551	1,050,425	
11 years	IUS	576	1,256,971	**IUS vs IUD: £3,489/pregnancy averted**
	Implant	585	1,344,278	Dominated by IUS
	IUD	610	1,139,234	
12 years	IUS	629	1,336,833	**IUS vs IUD: £2,928/pregnancy averted**
	Implant	638	1,424,189	Dominated by IUS
	IUD	667	1,225,501	
13 years	IUS	680	1,414,530	**IUS vs IUD: £2,498/pregnancy averted**
	Implant	689	1,552,016	Dominated by IUS
	IUD	722	1,309,296	
14 years	IUS	730	1,490,079	**IUS vs IUD: £2,159/pregnancy averted**
	Implant	739	1,627,730	Dominated by IUS
	IUD	776	1,390,690	
15 years	IUS	778	1,563,548	**IUS vs IUD: £1,884/pregnancy averted**
	Implant	788	1,701,410	Dominated by IUS
	IUD	828	1,469,754	

(f) Decreasing implant discontinuation rates by 10%

Duration of use	LARC method	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
1 year	Implant	13	258,912	**Implant vs IUD: £12,021/pregnancy averted**
	IUS	17	270,749	Dominated by implant
	IUD	18	195,442	
2 years	Implant	46	313,473	**Implant vs IUD: £6,440/pregnancy averted**
	IUD	55	256,572	
	IUS	57	337,093	Dominated by implant, IUD
3 years	Implant	91	383,506	**Implant vs IUD: £3,213/pregnancy averted**
	IUD	105	337,207	
	IUS	109	418,616	Dominated by implant, IUD
4 years	Implant	141	562,173	**Implant vs IUD: £5,349/pregnancy averted**
	IUD	166	432,018	
	IUS	167	508,869	Dominated by IUD
5 years	Implant	193	640,161	**Implant vs IUD: £2,711/pregnancy averted**
	IUS	228	603,534	Dominated by extended dominance
	IUD	232	534,555	
6 years	Implant	244	716,550	**Implant vs IUD: £1,438/pregnancy averted**
	IUS	290	767,736	Dominated by implant
	IUD	299	636,652	
7 years	Implant	293	873,256	**Implant vs IUD: £1,916/pregnancy averted**
	IUS	351	859,181	Dominated by extended dominance
	IUD	365	736,023	
8 years	Implant	342	946,080	**Implant vs IUD: £1,304/pregnancy averted**
	IUS	409	948,186	Dominated by implant
	IUD	429	832,635	
9 years	Implant	389	1,017,150	**Implant vs IUD: £573/pregnancy averted**
	IUS	466	1,034,800	Dominated by implant
	IUD	491	958,830	
10 years	Implant	435	1,158,512	**Implant vs IUD: 932/pregnancy averted**
	IUS	522	1,119,079	Dominated by extended dominance
	IUD	551	1,050,425	
11 years	Implant	480	1,226,164	**Implant vs IUD: £671/pregnancy averted**
	IUS	576	1,256,971	Dominated by implant
	IUD	610	1,139,234	
12 years	Implant	524	1,292,149	**Implant vs IUD: £467/pregnancy averted**
	IUS	629	1,336,833	Dominated by implant
	IUD	667	1,225,501	
13 years	Implant	567	1,419,673	**Implant vs IUD: £711/pregnancy averted**
	IUS	680	1,414,530	Dominated by extended dominance
	IUD	722	1,309,296	
14 years	Implant	608	1,482,418	**Implant vs IUD: £548/pregnancy averted**
	IUS	730	1,490,079	Dominated by implant
	IUD	776	1,390,690	
15 years	Implant	649	1,543,586	**Implant vs IUD: £413/pregnancy averted**
	IUS	778	1,563,548	Dominated by implant
	IUD	828	1,469,754	

D.3 Perfect use of male condom/COC

(a) Perfect use of male condom – results for 1 to 4 years of contraceptive use

1 year of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	14	262,117	Implant vs condom: £37,629/pregnancy averted
Implant/condom	14	287,764	Implant/condom vs condom: £42,255/pregnancy averted
IUS	17	270,749	IUS vs condom: £73,558/pregnancy averted
IUS/condom	17	295,998	IUS/condom vs condom: £82,106/pregnancy averted
IUD	18	195,442	IUD vs male condom: £83,248/pregnancy averted
IUD/condom	18	221,176	IUD/condom vs condom: £98,339/pregnancy averted
Condom	20	53,488	
Injectable	33	190,534	Dominated by condom
Injectable/condom	33	212,075	Dominated by condom alone

2 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Condom	39	105,167	
Implant	51	322,939	Dominated by condom
Implant/condom	51	368,213	Dominated by condom alone
IUD	55	256,572	Dominated by condom
IUD/condom	55	302,326	Dominated by condom alone
IUS	57	337,093	Dominated by condom
IUS/condom	57	381,382	Dominated by condom alone
Injectable	99	338,376	Dominated by condom
Injectable/condom	99	373,190	Dominated by condom alone

3 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Condom	58	155,098	
Implant	101	400,947	Dominated by condom
Implant/condom	101	462,023	Dominated by condom alone
IUD	105	337,207	Dominated by condom
IUD/condom	105	398,902	Dominated by condom alone
IUS	109	418,616	Dominated by condom
IUS/condom	109	478,387	Dominated by condom alone
Injectable	167	482,178	Dominated by condom
Injectable/condom	167	528,857	Dominated by condom alone

4 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Condom	76	203,341	
Implant	157	580,444	Dominated by condom
Implant/condom	157	654,972	Dominated by condom alone
IUD	166	432,018	Dominated by condom
IUD/condom	166	506,401	Dominated by condom alone
IUS	167	508,869	Dominated by condom
IUS/condom	167	581,728	Dominated by condom alone
Injectable	234	622,935	Dominated by condom
Injectable/condom	234	680,503	Dominated by condom alone

(b) Perfect use of COC – results for 1 to 15 years of contraceptive use

1 year of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	14	262,117	Implant vs COC: £6,195/pregnancy averted
IUS	17	270,749	IUS vs COC: £7,945/pregnancy averted
IUD	18	195,442	IUD vs COC: £2,858/pregnancy averted
COC	31	158,711	
Injectable	33	190,534	Dominated by COC

2 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	51	322,939	Implant vs COC: £977/pregnancy averted
IUD	55	256,572	IUD dominates COC
IUS	57	337,093	IUS vs COC: £1,551/pregnancy averted
COC	92	283,429	
Injectable	99	338,376	Dominated by COC

3 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	101	400,947	Implant dominates COC
IUD	105	337,207	IUD dominates COC
IUS	109	418,616	IUS vs COC: £180/pregnancy averted
COC	156	410,021	
Injectable	167	482,178	Dominated by COC

4 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	157	580,444	Implant vs COC: £637/pregnancy averted
IUD	166	432,018	IUD dominates COC
IUS	167	508,869	IUS dominates COC
COC	224	537,630	
Injectable	234	622,935	Dominated by COC

5 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	215	667,275	Implant vs COC: £22/pregnancy averted
IUS	228	603,534	IUS dominates COC
IUD	232	534,555	IUD dominates COC
COC	294	665,531	
Injectable	302	760,600	Dominated by COC

6 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	271	752,269	Implant dominates COC
IUS	290	767,736	IUS dominates COC
IUD	299	636,652	IUD dominates COC
COC	366	793,112	
Injectable	370	895,141	Dominated by COC

7 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	326	909,171	Implant dominates COC
IUS	351	859,181	IUS dominates COC
IUD	365	736,023	IUD dominates COC
Injectable	437	1,026,537	Injectable vs COC: £58,242/pregnancy averted
COC	439	919,863	

8 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	380	990,040	Implant dominates COC
IUS	409	948,186	IUS dominates COC
IUD	429	832,635	IUD dominates COC
Injectable	504	1,154,780	Injectable vs COC: £12,959/pregnancy averted
COC	512	1,045,355	

9 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	432	1,068,882	Implant dominates COC
IUS	466	1,034,800	IUS dominates COC
IUD	491	958,830	IUD dominates COC
Injectable	570	1,279,871	Injectable vs COC: £6,988/pregnancy averted
COC	586	1,169,238	

10 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	483	1,210,419	Implant dominates COC
IUS	522	1,119,079	IUS dominates COC
IUD	551	1,050,425	IUD dominates COC
Injectable	635	1,401,818	Injectable vs COC: £4,655/pregnancy averted
COC	659	1,291,222	

11 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	533	1,285,327	Implant dominates COC
IUS	576	1,256,971	IUS dominates COC
IUD	610	1,139,234	IUD dominates COC
Injectable	700	1,520,639	Injectable vs COC: £3,420/pregnancy averted
COC	732	1,411,073	

12 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	581	1,358,321	Implant dominates COC
IUS	629	1,336,833	IUS dominates COC
IUD	667	1,225,501	IUD dominates COC
Injectable	764	1,636,357	Injectable vs COC: £2,661/pregnancy averted
COC	804	1,528,602	

13 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	628	1,486,002	Implant dominates COC
IUS	680	1,414,530	IUS dominates COC
IUD	722	1,309,296	IUD dominates COC
Injectable	826	1,749,003	Injectable vs COC: £2,149/pregnancy averted
COC	875	1,643,663	

14 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	674	1,555,286	Implant dominates COC
IUS	730	1,490,079	IUS dominates COC
IUD	776	1,390,690	IUD dominates COC
Injectable	888	1,858,611	Injectable vs COC: £1,782/pregnancy averted
COC	945	1,756,143	

15 years of use	Total pregnancies	Total costs (£)	Incremental cost effectiveness ratio
Implant	719	1,622,769	Implant dominates COC
IUS	778	1,563,548	IUS dominates COC
IUD	828	1,469,754	IUD dominates COC
Injectable	948	1,965,220	Injectable vs COC: £1,507/pregnancy averted
COC	1014	1,865,957	

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Index

DMPA = depot medroxyprogesterone acetate
IUD = intrauterine device
IUS = intrauterine system
LNG-IUS = levonorgestrel intrauterine system
NET-EN = norithesterone enantate
POIC = progestogen-only injectable contraceptives
POSDI = progestogen-only subdermal implants