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Review

Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness

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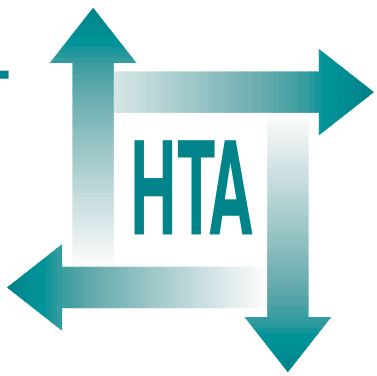
Health Technology Assessment
NHS R&D HTA Programme



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Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Pharmaceutical Panel and funded as project number 95/41/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

Glossary

Allocation concealment Allocation concealment is when individuals taking part in a study are randomly allocated to a treatment (e.g. a contraceptive method) and neither they nor the investigator know which treatment is given. This prevents the bias that could arise if investigators or the individuals recruited onto a trial were selecting the treatments.

Amenorrhoea Amenorrhoea is usually defined as absence of a period for at least 6 months (or absence of three menstrual cycles), not caused by pregnancy, in women of reproductive age.

Cohort study A cohort study is one in which a group of individuals, who differ in their exposure to an intervention or risk factor, are followed up over time to determine the incidence of outcomes. The association between exposure and outcome is then estimated. For example, women who chose Norplant are compared with women who chose the IUD and followed up for 1 year to see if any pregnancies occur.

Confidence interval A confidence interval is a range within which, given a degree of certainty/confidence (e.g. 95%), the 'true' value or summary measure of the population can be expected to lie.

Confounding Confounding is the distortion of an estimate of the association between an exposure (e.g. contraceptive method) and outcome (e.g. pregnancy) because of the association of the exposure with another factor (e.g. age) that influences the outcome under investigation. Confounding can either be dealt with in the study design or later when conducting the statistical analysis. In theory, RCTs remove the problem of confounding.

Depomedroxyprogesterone acetate Depomedroxyprogesterone acetate (DMPA), which is marketed as Depo-Provera®, is a contraceptive injection of 150 mg medroxyprogesterone given as an intramuscular depot every 12 weeks. The effect, like that of the combined contraceptive pill, is to stop ovulation in most women.

Dysmenorrhoea Dysmenorrhoea is defined as painful menstruation.

Effect modifiers These are factors that could alter the results (e.g. whether or not a woman had pre-treatment contraceptive counselling).

Fecundibility Fecundibility refers to the ability to conceive.

Fixed effect approach A fixed effect approach in meta-analysis assumes that the data collected in the separated trials can be used to estimate the same effect size parameter (a parameter that underlies all the studies in the meta-analysis) and that any variation between effect sizes is due to random error within the studies. Thus each study produces an estimate of common, or fixed, effect size, assuming the 'true' population value in each of the studies is the same (i.e. that is there is no heterogeneity between studies; see 'Heterogeneity').

Heterogeneity Heterogeneity in meta-analysis refers to the variability in effect sizes between the studies. Although the studies ask similar questions they will not be identical. The result of these differences is that the various studies estimate different parameters. There are tests to determine whether the variability is greater than expected or due to chance alone. The random effects approach is a method for accounting for unexplained heterogeneity (see 'Random effects approach').

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Menorrhagia Menorrhagia refers to heavy menstrual blood loss.

Intervention studies In these studies the investigator allocates individuals (or groups) who have similar characteristics to an intervention (e.g. a new contraceptive method) or to a control (e.g. a standard contraceptive method), and compares the incidence of outcomes of interest (e.g. pregnancy rates) between the two groups.

Levonorgestrel Levonorgestrel is a potent progestogen and currently the most frequently used in the long-acting contraceptives, whether subdermal or intrauterine.

Life tables Life tables are used to measure survival (or failure) of individuals/groups over time and are frequently used in contraceptive research to measure pregnancy and continuation of use. They are calculated by working out the monthly probability of an outcome (e.g. reason for discontinuing a contraceptive method) and multiplying the monthly probabilities to establish the probability of the outcome over time (i.e. at 1 year follow-up, 2 year follow-up). This method is more accurately defined as multiple decrement life-table analysis. However, single decrement life-table analysis is recommended for contraceptive research because it excludes individuals, at the time of discontinuation, who stop using a method for reasons other than the one being measured (e.g. when discontinuing a method due to accidental pregnancy only).

Meta-analysis Meta-analysis is the statistical technique that is used to combine the results of a collection of studies into a single numerical estimate.

Norgestrel Potent progestogen with a long half-life and somewhat anti-oestogen effects, used in combined and long-acting contraceptives. It was synthesised by the pharmaceutical company Wyeth in about 1980.

Nova-T (Novagard® Copper) intrauterine device (IUD) The Nova-T is a T-shaped IUD with copper wire (having a core of silver) wound around its vertical limb and with slightly down-turned ends to its transverse arms.

Nulliparous Nulliparous means never having given birth.

Oligomenorrhoea Oligomenorrhoea is usually defined as menstrual intervals between 6 weeks and 6 months, although definitions do vary.

Parous Parous means having given birth.

Pearl index The Pearl index is a statistical measure that provides a rate per 100 women years of follow-up and is calculated by dividing the number of events (such as pregnancy) by the number of women months of follow-up and multiplying them by 1200 (or 1300 if the measurement is calculated by menstrual cycles rather than months).

Prolonged bleeding Prolonged bleeding is usually defined by women to describe menstrual bleeding that is longer than the norm (some medical professionals would say longer than 10 days per menstrual calendar).

Progestogen Progestogen is a steroid hormone which has a contraceptive effect.

Random effects approach This method of meta-analysis, in contrast to a fixed effects model, assumes that the true effect sizes for outcomes are not fixed and that any variation between effect sizes is due to random error within the studies as well as due to random error between the different studies. This method is more conservative than the fixed effects approach and therefore the confidence intervals will be wider.

Randomised controlled trials Randomised controlled trials are a type of intervention study and are considered to be the 'gold standard' because they minimise bias as study participants are randomly allocated (i.e. allocation is determined by chance, such as by throwing a coin) to intervention groups rather than allocation being chosen by either the participant or the investigator.

Rate ratio The rate ratio is calculated by dividing the incidence rate in the intervention group by the incidence rate in the control group. Rate is expressed in units of person time (e.g. women months – the total number of months women continued to be followed up in a study).

Risk ratio The risk ratio is calculated by dividing the risk of an event in the intervention group by the risk of an event in the control group. Risk is defined as the proportion of individuals in a study who are initially event-free (e.g. have a regular menstrual cycle) and who experience an event (e.g. amenorrhoea) within a specific time period.

Sensitivity analysis Sensitivity analysis allows investigation of the robustness of the results by seeing how the conclusions differ when one or more of the assumptions used in the review is varied (e.g. study quality).

Spotting Spotting refers to light bleeding between periods.

Standard deviation and standard error of the mean These are both measures of the variance. The standard deviation describes how measurements from individuals naturally differ. The standard error of the mean does not directly describe the variability between individuals, but describes how accurately the mean value for a group of individuals has been estimated.

Subgroup analysis Subgroup analyses are meta-analyses of subsets of studies or subsets of study participants, so that the summary effect sizes can be compared (e.g. comparing the summary effect size of the meta-analysis of pregnancy rates in parous women with the summary effect size of the meta-analysis pregnancy rates in nulliparous women).

List of abbreviations

AR	attributable risk*
CI	confidence interval
CuT	copper T
DMPA	depomedroxyprogesterone acetate
d-Ng	d-norgestrel*
fpa	formerly the Family Planning Association
FPC	family planning clinic
GP	general practitioner
IUD	intrauterine device
IUS	intrauterine system
LNG	levonorgestrel
LT	life table*
MA	megestrol acetate*
N/A	not applicable*
non-RCT	non-randomised controlled trial
PI	Pearl index
PID	pelvic inflammatory disease
PR	pregnancy rate*
RCT	randomised controlled trial
RR	relative risk*
SD	standard deviation
SE	standard error
WHO	World Health Organization

* Used only in tables

Executive summary

Background

Research on progestogen-only contraceptive subdermal implants and hormonally impregnated intrauterine systems (IUSs) started in the mid-1970s, with some, including Norplant® and the LNG-20 IUS (Mirena®), receiving licences for use in the UK by the early 1990s. Implanon® became available in the UK in autumn 1999. Since this review was commissioned Norplant has been withdrawn from the UK market because of adverse publicity.

Aims

- To assess the contraceptive efficacy, tolerability and acceptability of subdermal implants and IUSs in comparison with other reversible contraceptive methods.
- To use these data to determine the relative cost-effectiveness.

Methods

Data sources

Literature was identified through electronic database searches, reference lists and contacting individuals/organisations working in the field.

Study selection

All prospective intervention studies that compared subdermal implants or IUSs with other forms of reversible contraceptives and reported pre-determined outcomes in women of reproductive years were included. The primary outcomes measures reviewed were pregnancy due to method/user failure and continuation of contraceptive method.

Data extraction

The quality assessment of studies and data extraction were completed independently by two blinded reviewers. A quality check list was designed to identify general methodological and contraceptive-specific factors which could bias results. Events per women months and single decrement life-table probabilities were extracted for pregnancy, continuation, adverse events and reasons for discontinuation. Events per total number of women at follow-up were collected for hormonal side-effects, menstrual disturbance, and planned pregnancy after discontinuation of method.

Data synthesis

When appropriate, data were pooled at the same time points of follow-up and rate ratios were calculated to determine the relative effectiveness of contraceptive methods. For single decrement life-table probabilities, probability differences were pooled to determine the absolute difference in effectiveness. Interventions were combined only if the contraceptive methods were similar (e.g. studies comparing IUSs with copper intrauterine devices (IUDs) > 250 mm^3 were combined, and studies comparing IUSs with copper-bearing IUDs ≤ 250 mm^3 were combined). (The categorisation of copper-bearing IUDs was based on the surface area of the copper wire.)

Results

Subdermal implants

Thirty-four comparative studies met the inclusion criteria. The majority of studies were comparisons of different types of implant, although there was a broader range of comparisons in the non-randomised controlled trials (non-RCTs). In many of the non-RCT studies the intervention groups were often dissimilar at baseline. It was possible to combine the data from only a few studies as it was deemed inappropriate to use data from investigations of prototypes.

- For Norplant, the most common comparison was with other types of subdermal implant, followed by comparisons with IUDs. There was no significant difference in the pregnancy rate among users of Norplant compared with users of other contraceptive methods (Level 1a* for Norplant versus Implanon – there were no pregnancies with either method; level III versus other methods). Norplant users were about twice as likely to continue with the

*Type of evidence (based on Agency for Health Care Policy and Research (USA), 1994). Ia: evidence obtained from the meta-analysis of RCTs. Ib Evidence obtained from at least one RCT. IIa: evidence obtained from at least one well-designed controlled study without randomisation. IIb: evidence from at least one other type of well-designed quasi-experimental study. III: evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies.

method compared with women using oral contraceptive pills, vaginal rings or depomedroxyprogesterone acetate (DMPA) injections (III).
- There was no evidence of differences between Norplant users and users of other contraceptive methods in relation to planned pregnancy following removal (IIa), hormonal side-effects (III), or adverse clinical events (Ib). Norplant users were significantly less likely than IUD ≤ 250 mm^3 users to expel the device (III). When Norplant was compared with IUDs > 250 mm^3, there were significantly lower rates of dysmenorrhoea, spotting, menorrhagia and prolonged bleeding (III). Norplant users were significantly more likely to experience amenorrhoea than users of IUDs > 250 mm^3 or the contraceptive pill (III).
- Norplant users were 90% less likely to discontinue for menstrual reasons compared with women having DMPA injections (III). The only other significant difference observed was that Norplant users were less likely than pill uses to discontinue the method for personal reasons.

Hormonally impregnated IUSs
- Twenty-nine intervention studies with IUSs met the inclusion criteria. With one exception (a study that compared the LNG-20 IUS with Norplant-2) all were comparisons between different types of IUS or between IUSs and IUDs. It was possible to pool data from only a few studies.
- There was no evidence that LNG-20 IUS users differed from users of IUDs > 250 mm^3 (Ia) in terms of unplanned pregnancy. In the comparison of the LNG-20 IUS with IUDs ≤ 250 mm^3 (Ia), LNG-20 IUS users were significantly less likely to have either intrauterine or extrauterine pregnancies when rate ratios were calculated (i.e. events per women months).
- Calculation of differences in single decrement life-table probabilities indicated that after 5 years women assigned to the LNG-20 IUS were significantly less likely to continue with the method than were women assigned to the IUD > 250 mm^3. However, this difference was not evident when rate ratios were pooled (Ia).
- LNG-20 IUS users were more likely to experience amenorrhoea (Ib) and device expulsion (Ia) compared with IUD > 250 mm^3 users. There was no evidence of other significant differences between methods, in terms of the occurrence of acne, headaches, breast tenderness, nausea, prolonged bleeding, embedded device, or pelvic inflammatory disease (Ib).
- LNG-20 IUS users were more likely than other IUD users to discontinue because of hormonal side-effects (Ia) or menstrual disturbance (Ib) (specifically amenorrhoea [Ib]). No other significant differences in reasons for discontinuation were observed.

Cost-effectiveness analysis
The economic evaluation was informed by the results of the systematic review and meta-analyses, which provided data on the effectiveness and the duration of use of the compared alternatives.

Generally the cost-effectiveness ratios for subdermal implants and IUSs were quite high, indicating that they were on balance more costly per pregnancy averted than the contraceptive methods with which they were compared. This was explained by the low incremental effectiveness of these methods relative to the other contraceptive methods.

Conclusions and recommendations

There was insufficient evidence from the comparative studies included in these systematic reviews to suggest that one type of subdermal implant was any more or less effective in preventing pregnancy than another, that implants were any more or less effective than the other methods with which they were compared, or that the LNG-20 IUS was any more or less effective than IUDs > 250 mm^3. LNG-20 IUS users were significantly less likely to experience either intrauterine or extrauterine pregnancies than were IUD ≤ 250 mm^3 users. Women using the LNG-20 IUS were more likely to experience amenorrhoea, and this event was a notable reason for discontinuation of IUSs.

Poor study design, lack of clarity in measurement of contraceptive effectiveness and heterogeneity between studies hindered synthesis of data. The following recommendations are made on the basis of the evidence from these reviews.

1. Standardisation of methods and measurements used in contraceptive research should be encouraged.
2. Well-designed prospective cohort studies should be carried out to follow up women using different contraceptive methods.
3. An RCT is required to assess the impact of counselling on discontinuation rates of subdermal implants and IUSs, particularly in relation to the effect of amenorrhoea.
4. There should be consumer involvement in the development of contraceptive research to identify user-related questions.
5. Evaluation should be carried out to determine the most effective training for healthcare workers in the insertion and removal of implantable contraceptives.
6. Economic endpoints should be included in primary research on methods of contraception.

Chapter 1
Background

Introduction

Each year more than 6 million people in the UK use family planning services provided by NHS-funded family planning clinics (FPCs) or general practitioners (GPs). In 1991, this service was estimated to cost £159.7 million, accounting for 0.5% of the total public expenditure on healthcare.[1]

In the last few years, several new progestogen-only implantable contraceptive methods have been licensed for use in the UK. These include Norplant®, a subdermal levonorgestrel (LNG) contraceptive implant and Mirena®, an LNG-impregnated intrauterine system (IUS). These contraceptive methods are compliance-free, with users having consciously to discontinue using them to become pregnant, rather than taking a proactive daily decision to avoid conception, and so pregnancy associated with user failure is uncommon. This represents a far better 'default' state than exists with common alternatives such as the oral contraceptive pill (the 'pill') or the condom.

The main focus of this review is implantable contraceptive methods: the subdermal implants (Norplant, Norplant-2 and Implanon®) and the hormonally impregnated IUSs (Mirena and Progestasert).

Rationale for the reviews

The uptake of implantable contraceptives in the UK has been poor and these new methods have, so far, been restricted to certain user groups. A number of reasons have been proposed to explain the poor uptake among with women using family planning services.

- The initial cost of these methods is high (for 5 years contraceptive cover, Norplant £179, Mirena £99). Health professionals have been reluctant to offer these methods because of concerns about the high cost if women choose to terminate use early.
- Insertion and removal of implants requires formal training.
- GPs do not receive an item-for-service payment for implantation of these devices, in contrast with practice for other methods. They were advised by the British Medical Association not to prescribe Norplant until funding issues had been resolved.
- Consumer demand was affected by media publicity surrounding problem side-effects and a few high profile cases of difficult removal with Norplant.

Hormonal contraceptive implants

Research on progestogen-only contraceptive implants started in 1974. Norplant underwent its preintroductory trial in 1980 and was the first contraceptive implant to be granted a licence in the UK.

Norplant

Norplant is a long-term, low-dose, reversible contraceptive progestogen implant. Its contraceptive effect lasts for 5 years, after which the implant should be removed. It first became available in the UK on NHS prescription in October 1993. Over 54,000 women in the UK have used Norplant. Since this review was commissioned, Norplant has been withdrawn from the market in the UK. A press release issued by Hoechst Marion Roussel Ltd stated that its withdrawal was a commercial decision made by the company because of poor publicity and a high-profile legal suit, not because of concerns about the safety and effectiveness of Norplant.[2] The compensation claim by 275 Norplant users over alleged side-effects collapsed after funding from the Legal Aid Board was withdrawn.[3] Norplant will continue to be licensed in the UK for the next 5 years to take account of the women who have recently had it inserted and continue to use it as their contraceptive method. Norplant is still available and used in other countries, with over 6 million women using it worldwide, including 1 million in the USA.[2]

Norplant consists of six small, flexible, sealed capsules made from polydimethylsiloxane (medical grade elastomer, silastic) which are placed in a fan-shaped pattern in the subdermal

layer of the upper inner aspect of the woman's non-dominant arm. Each Norplant capsule is 34 mm long and 2.4 mm in diameter and contains 38 mg of the progestogen LNG.[4] Approximately 85 µg LNG/day is released initially, and this decreases to 50 µg/day by 6 months and 35 µg/day by 18 months.[5]

The net ingredient cost of Norplant (i.e. the initial cost of the product itself) is £179.

Norplant-2

Norplant-2 (Jodelle) is not available in the UK, although it is licensed for use in other countries. As a consequence of the withdrawal of Norplant from the UK market, it is unlikely to be marketed in the UK. Norplant-2 consists of two silastic rods containing LNG and appears to provide effective contraceptive cover for 3 years.[5] The reduced number of rods may make it more acceptable to users than Norplant.

Implanon

Implanon is a single 40-mm thread containing 60 mg of the third-generation progestogen 3-keto-desogestrel which is released at a rate of 30 µg/day.[6] It is inserted through a disposable wide-bore needle. Implanon has undergone pre-marketing trials and appears to be effective for 3 years. It has received European licensing and was launched in the UK in the autumn of 1999.[7]

Hormone-impregnated IUSs

In the 1970s a new approach to the delivery of hormonal contraception was developed. Research on hormonally medicated intrauterine contraceptive devices showed that the addition of a progestogen to an inert intrauterine device (IUD) improved its contraceptive action.

Progestasert

The first hormone-impregnated IUS to be marketed in the UK was Progestasert. It has a plastic T-shaped frame with a 32-mm horizontal cross bar and a 36-mm vertical stem. The vertical stem holds 38 mg of progesterone within a silicone base and when Progestasert is placed in the uterus it will release 65 µg of progesterone/day. Its contraceptive action lasts for 12–18 months[8] and is achieved by a combination of endometrial suppression, which prevents implantation, and thickening of the cervical mucus, which prevents sperm penetration. Ovulation, however, is not affected, and normal hormonal cyclical patterns have been demonstrated in users.

Although Progesasert is still used in other countries, its UK licence was not renewed by the company in light of its chief disadvantages. These included:

- yearly reinsertions with the associated risk of pelvic inflammatory disease (PID)
- increased ectopic pregnancy rate when compared with copper-bearing IUDs
- some women experiencing persistent menstrual spotting.

LNG-20 IUS (Mirena)

The LNG-20 IUS (Mirena) has been available in the UK since May 1995 and is licensed for contraceptive use in 25 other countries.[9] Mirena has a T-shaped plastic frame 32-mm long with a reservoir on the vertical stem containing 52 mg LNG mixed with polydimethylsiloxane.[10] This allows a steady, local release of 20 µg LNG/day through the rate-limiting surface membrane. The LNG-20 IUS has a contraceptive licence for 5 years in the UK.

Insertion may require local anaesthesia and dilatation of the cervical canal in nulliparous or peri-menopausal woman. It is an invasive procedure which may be unacceptable to some women.

The LNG-20 IUS is more expensive than copper-bearing IUDs (£99 compared with approximately £9), but it offers considerable non-contraceptive benefits, particularly in women with heavy periods, and may provide an alternative to hysterectomy.[11,12]

Methodological issues in measuring contraceptive efficacy

Contraceptive research has its specific methodological difficulties. Fortunately, recommendations have been provided on how to address these problems when conducting contraceptive studies.[13–15]

Factors affecting risk of contraceptive failure

Definition of failure

Contraceptive failure may be the result of method failure (attributed to failure of the method itself when it has been correctly used), user failure (attributed to imperfect use of the method by the user) or a combination of method and user failure. Perfect use of a contraceptive method is defined as both the

consistent and the correct use of the method from its initiation.[16]

In practice, when comparing women who are using subdermal implants with those who are using condoms, user failure is not a factor in the first group, whereas it is in the second group. The failure rates, whether they are due to method only, user only or both method and user, reflect what happens in the real world. However, measurement of efficacy (i.e. perfect use) in comparison with user-effectiveness outcomes does provide useful information to the contraceptive user.

Description of contraceptive method before study enrolment

Information about the contraceptive method being used before enrolment is important for two reasons. Firstly, women who use hormonal contraceptives immediately before enrolment may continue to have contraceptive benefit from them for the first 3 months of the study and therefore their fecundity is greatly reduced during this period. Secondly, it is important that women should not already be on the investigated method before enrolment as this may affect the measurement of effectiveness, tolerability and acceptability outcomes. Among women who are recruited to prospective cohorts, past experience of contraceptive methods is likely to influence their subsequent choice of method, therefore introducing selection bias. Unfortunately, data on contraceptive history are rarely presented and therefore it is impossible to control for this in the analysis unless the cohort has been naive to all methods of preventing pregnancy, which is unlikely.

Fecundity of the population

Additional factors, such as age and previous parity, can provide indications of the fecundity of an investigated population. For example, the risk of pregnancy for a woman in her late thirties is much lower than for a woman in her early twenties.

Units used for measuring contraceptive failure

Extensive reviews have helped to provide greater clarity in the understanding of the various methods and terminologies used to measure contraceptive efficacy and have examined their relative advantages and disadvantages.[14,17] In brief, there are generally two methods which have been adopted, the Pearl index (PI) and life tables. The PI is the older method.[18] It provides a rate per women years and is calculated by dividing the number of events (such as pregnancy) by the total number of women months and multiplying by 1200 (or 1300 if the measurement is calculated by menstrual cycle). This method has been criticised because it does not account for the variation in risk of pregnancy over time – women are at higher risk of becoming pregnant in the early stages of the investigation.[19,20] Consequently, PIs calculated from, say, 100 women observed for 1 year will differ inappropriately from those calculated from ten women observed for 10 years. A further problem with the PI is that it does not account for variation in loss to follow-up.

Life-table probabilities are the most appropriate way to report contraceptive data because they focus on investigation of time elapsing before events happen (often described as survival data or time-to-event data in the statistical literature). Confusion arises because inconsistent methods are used to define and calculate these probabilities (see *Table 1*). In brief, multiple decrement life-table probabilities are calculated by working out the monthly probability of, for example, discontinuation for any reason, and multiplying these to establish the probability of discontinuation over a fixed period (e.g. at 6 months follow-up, 1 year follow-up, and so on). However, single decrement life-table probabilities are recommended. These are calculated in the same way as multiple decrement life-table probabilities but for only a single reason (i.e. at the time of discontinuation they censor data for women who discontinue a method

TABLE 1 *Definitions of commonly cited terminology used for calculating life-table rates*

Definition	Life-table terms				
	Potter, 1967[19]	**Tietze & Lewit, 1968[21]**	**Azen, *et al.*, 1977[22]**	**Chiang, 1968[23]**	**Other terms used**
Overall probability of event (e.g. all discontinuations)	Net	Net	Crude	Crude	Multiple decrement Competing
Probability of event removing other risks (e.g. discontinuation due to accidental pregnancy only)	Gross	Gross	Net	Net	Single decrement Noncompeting

for reasons other than the one being measured). Unfortunately, as *Table 1* illustrates, it is often impossible to distinguish which method has been used if it is not clearly stated by the authors because 'net' can refer to single or multiple decrement probabilities.

For the purpose of this review, the term 'multiple decrement life-table probability' is used when referring to overall probability of an event and the term 'single decrement life-table probability' is used when referring to the probability of an event when other risks have been removed.

Analysis of contraceptive failure

Separate analysis of early spontaneous aborted pregnancies

If laboratory studies are used to detect pregnancies which are later spontaneously aborted in the early stages, the early spontaneous abortions should be reported separately because otherwise the pregnancy rate will be exaggerated in comparison with (most) other studies which have not used the same techniques. In addition, studies with more rigorous follow-up are likely to detect early pregnancies which may spontaneously abort. These early pregnancies and subsequent spontaneous abortions may be undetected by women and are less likely to be picked up by less frequent follow-up visits. This latter point should be considered when interpreting results.

'Active' follow-up

Tietze[21] recommends that analysis of follow-up visits should be delayed for a few months so that any undetected pregnancies which have occurred just before the last follow-up period can be included in the results.

Aims of the systematic reviews

The aims of the systematic reviews were:

- to assess the contraceptive efficacy, tolerability and acceptability of subdermal implantable contraceptives and IUSs in comparison with other reversible methods of contraception in women of reproductive age
- to use these data to determine the cost-effectiveness of subdermal implantable contraceptives and IUSs in comparision with relevant contraceptive alternatives.

Chapter 2
Methods

Objectives

The objectives of the reviews were to determine the effectiveness, side-effects and cost-effectiveness of subdermal implants and IUSs, and to evaluate the ease of insertion and removal of these contraceptive devices (including evaluating the effects of operator skill on the effectiveness of the method).

The following hypotheses were to be tested.

- Implants/IUSs are as effective as other reversible contraceptive methods in preventing unwanted pregnancy.
- Implants/IUSs have rates of side-effects that are similar to those associated with other reversible contraceptive methods.
- There is no association between operator skill and contraceptive effectiveness.
- The costs of implant/IUS provision are the same as those of other relevant methods in preventing unwanted pregnancy.

Study selection

Studies were selected for inclusion in the systematic reviews if they met the criteria identified below.

Types of study

The following types of study were included:

- all randomised controlled trials (RCTs) and controlled clinical (i.e. quasi-randomised) trials that compared (a) subdermal implants or (b) hormone-impregnated IUSs with other forms of reversible contraceptives.
- non-randomised prospective cohorts that compared (a) subdermal implants or (b) hormone-impregnated IUSs with other forms of reversible contraceptives.

Types of participant

All studies that included women of reproductive years were eligible for inclusion in the reviews.

Types of intervention

Subdermal implants

Studies eligible for inclusion compared subdermal implants with:

- non-hormonal IUDs
- barrier contraceptives
- oral contraceptives
- injectable contraceptives
- hormone-releasing IUSs.

Studies that reported comparisons of different subdermal implants (e.g. Norplant with Norplant-2) were also included.

Hormone-releasing IUSs

Studies eligible for inclusion compared hormone-releasing IUSs with:

- non-hormonal IUDs
- barrier contraceptives
- oral contraceptives
- injectable contraceptives
- subdermal implants.

Studies that reported comparisons of different IUSs (e.g. Mirena with Progestasert) were also included.

Types of outcome

The outcomes listed below were pre-determined by members of the Steering Group (appendix 1) as being clinically meaningful.

Primary outcome measures

- Pregnancy due to method/user failure at 1, 2, 3, 4 and 5 years after starting the contraceptive method
- Continuation at 1, 2, 3, 4 and 5 years after starting the contraceptive method

Secondary outcome measures

- Planned pregnancy after discontinuation of contraceptive method at 1 and 2 years
- Failed implant removal
- Hormonal side-effects
- Menstrual disturbance
- Local device problems
- Adverse clinical events
- Reasons for discontinuation

The following were also examined:

- effect of preinsertion counselling on removal rate at 1, 2, 3, 4 and 5 years

- effect of operator training/skill level on rate of failed implant removal
- effect of parity on removal rate at 1, 2, 3, 4 and 5 years
- effect of age on removal rate at 1, 2, 3, 4 and 5 years.

A list of all the outcomes for which data were collected is provided in appendix 2.

Search strategy

The following electronic databases were searched from 1972 (or the first year recorded on the database if after 1972) to July 1998: MEDLINE, EMBASE, Cochrane Trials Register, PsycLIT, POPLINE and the database at the library of the fpa (formerly the Family Planning Association). A search strategy was designed using free text and thesaurus terms (see appendix 3) and adapted for each of the databases.

Hard copies of relevant papers were obtained and their reference lists were checked to identify any further studies.

Requests for unpublished data were made to individuals and organisations working in the implantable contraceptive field (i.e. practitioners, academics and pharmaceutical companies).

Quality assessment

Quality assessment forms were designed, and included general methodological factors which may bias study results, as well as some contraceptive-specific factors recommended by Trussell and colleagues[14] (*Box 1*).

The reviewers, who were blinded to both source and authors, carried out independent assessments of the quality of papers and reviewer agreement was rated. When necessary, authors were contacted and asked to provide further information on quality factors, such as clarification of study design or life-table measurements. Quality factors were collected with the aim of assessing their effect on results through subgroup analysis.

BOX 1 Quality assessment check list

RCTs	Non-randomised prospective cohort comparisons
1. Method of randomisation described	1. Intervention and control groups comparable at entry
2. Description of hormonal contraceptive method or pregnancy immediately before study enrolment	2. Description of hormonal contraceptive method or pregnancy immediately before study enrolment
3. Allocation concealment	3. Blinded assessment of outcomes
4. Blinded assessment of outcomes	4. Groups treated identically other than named intervention
5. Groups treated identically other than named intervention	5. Follow-up similar in intervention and control groups
6. Description of women who withdrew or were lost to follow-up provided	6. Description of women who withdrew or were lost to follow-up provided
7. Method (with reference) used to analyse pregnancy and continuation of methods	7. Control for confounding in study design (e.g. matching or restriction) or analysis (e.g. stratification or regression)
8. Description of contraceptive failure provided (i.e. user or method failure or both)	8. Method (with reference) used to analyse pregnancy and continuation of methods
9. Active follow-up	9. Description of contraceptive failure provided (i.e. user or method failure or both)
	10. Active follow-up

Data extraction

Two reviewers (RF and FC), who were were blinded to both source and authors, independently extracted data onto specially designed data collection forms (see appendix 4). Single decrement life-table probabilities with their standard errors (SEs) and events per women months (akin to the PI rate) were collected for each outcome at specific follow-up points (i.e. 1 year, 2 years, and so on). Differences were resolved by discussion and consensus. Data were extracted from non-English articles by one of the reviewers (RF) working with a translator.

It was decided to collect both single decrement life-table probabilities and events per women months as ways of reporting event rates, because although single decrement probabilities are the ideal[15] they were not commonly used in the studies, whereas there usually was sufficient information in the papers to collect events per women months. Of those papers which had reported single decrement probabilities, only a few had given SEs, a necessity for meta-analysis. Authors (of the RCTs only) who had used single decrement probabilities but had not given their SEs were contacted and asked to provide them where possible.

Menstrual disturbance outcomes were only collected if investigators had stipulated that they had been measured over 90-day intervals as recommended by Rodriguez and colleagues.[24] Number of events and total number of women at each 90-day interval were recorded so that risk ratios for menstrual disturbance outcomes could be calculated.

Data on hormonal side-effects and planned pregnancy after discontinuation of contraceptive method were collected at yearly time intervals. Data on these outcomes were collected only if the investigators provided number of events and total number of women at follow-up, so that risk ratios for each of the side-effects identified in the protocol could be determined. Data on weight change were collected by extracting the mean weight difference (with its standard deviation, SD) between the start of the study and follow-up time points.

Qualitative synthesis

For each study, a description of the demographic characteristics of the participants, the interventions, environmental and geographical factors which may influence findings, the quality of the study, and the measured outcomes were noted, so that decisions could be made about the results of individual studies and about whether they could be included in the combined data.

Studies were only combined when the interventions were comparable, such as Norplant versus oral contraceptives or Norplant versus injectable contraceptives (see 'Types of intervention', page 5). Non-hormonal IUDs were divided into three categories for the purpose of data synthesis. The first category, defined as copper-bearing IUDs > 250 mm^3, included Copper T (CuT) 380A and CuT 380Ag IUDs. The second category, defined as copper-bearing IUDs ≤ 250 mm^3, included the Nova-T, Multiload, CuT 200 and CuT 220 IUDs. The third category included inert IUDs. The categorisation of the copper-medicated IUDs was based on the surface area of the copper wire.

Quantitative synthesis

Data from RCTs and the non-RCT cohort studies were combined and subgroup analysis was conducted to investigate the effect this had on the summary effect size.

Methods for calculating study effect size

Events per women months

To obtain a summary effect size of an event per women months the rate ratios of the case and control events were combined.

The following calculations,[25] using pregnancy events as an example, were done for each outcome for which it had been possible to collect number of events over time.

Where number of pregnancies for cases = A, and for controls = B, and the follow-up period for cases = S and for controls = T, then:

$$\text{log rate ratio} = \log \frac{A / S}{B / T}$$

with the approximate estimate of the variance being:

$$\text{Var}[\log(\omega)] \approx \frac{1}{A + 1/2} + \frac{1}{B + 1/2}$$

Once the log rate ratios and their variances had been calculated for each study, it was then possible to calculate the inverse weighted average of the log rate ratios. The logarithmic scale was used to improve the normal distribution of the data. Events were only combined if they were measured over the same follow-up period (i.e. 1 year, 2 years, and so on) because of their variability over time. In situations where there were no events in one of the contraceptive comparison groups, continuity correction was implemented by adding a half to each event cell for the purpose of data synthesis.

Life-table probabilities

To synthesise single decrement life-table probabilities, it was necessary to calculate the measurement of true effect. This was done by subtracting the control group probability from

the intervention group probability ($prob_I - prob_C$). The SE for the measurement of true effect was then calculated by the following formula:

$$se(prob_I - prob_C) = \sqrt{[se(prob_I)^2 + se(prob_C)^2]}$$

If there was a probability of zero in one of the groups, its SE was assumed to be the same as the SE of the probability in the comparison group.

The inverse weighted average of the probability differences was then calculated.

Risk ratios and mean difference

To obtain pooled estimates for risk ratios and mean differences, the inverse variance weighted average was used with the sample log risk ratio and the sample mean difference, respectively, calculated from each study.[26] Continuity correction was done when necessary as described above for the calculated risk ratios.

Microsoft Excel was used to calculate the pooled effect sizes. Confidence interval (CI) plots were designed using S-PLUS.[27]

Heterogeneity

The degree of heterogeneity was investigated. A random effects approach was used for the meta-analysis. The summary effect size from a random effects approach coincides with a fixed effect approach when there is no heterogeneity between studies.[28] When the random effects approach estimated that the amount of heterogeneity was non-zero (the method of moments estimate of heterogeneity parameter), different results were given. Instances of heterogeneity are noted in the results.

Publication bias

It was intended to use funnel plots to examine the extent to which publication bias affected selection of studies for inclusion in the review. A linear regression approach was to be used to measure any funnel plot asymmetry.[29] If study selection appeared to have been compromised by publication bias, an estimate of how serious the bias would have to be to change the results of the review was to be made and reported.

Economic analysis

Using data derived from the meta-analyses

The economic evaluation was conducted using the results of the systematic review and meta-analyses. The aim of the economic evaluation was to estimate the effects, costs and cost-effectiveness of subdermal implants and IUSs in comparison with other contraceptive methods used in the UK. The perspective taken was that of the UK NHS. Effects were measured in terms of pregnancies averted by subdermal implants and IUSs relative to other contraceptive methods. Costs were measured in terms of the direct cost of service provision and cost savings from pregnancies averted. Cost-effectiveness was measured in terms of incremental cost per pregnancy averted. The form of the economic evaluation was therefore cost-effectiveness analysis.

Comparisons were made between subdermal implants or IUSs and other contraceptive methods. The exact options compared in the economic evaluation were determined using four criteria.

1. Only contraceptive methods currently available in the UK were included. It was not possible to include other methods since no UK data on their costs were available. For example, Progestasert was not included in the economic evaluation for this reason.
2. Only contraceptive methods included in the meta-analysis were included in the economic evaluation. It was not possible to include other methods because no reliable evidence was available on their effectiveness relative to subdermal implants or IUSs. For example, contraceptive diaphragms were not included in the economic evaluation for this reason.
3. Comparisons in the economic evaluation were made only between options compared directly in the clinical trials pooled in the meta-analysis. It was not possible to make other comparisons since no reliable evidence was available on relative effectiveness. For example, the LNG-20 IUS was not compared directly with 'no method' in the economic evaluation because these alternatives were not compared directly in a head-to-head trial included in the meta-analysis.
4. Comparisons in the economic evaluation were made between options only across time periods for which data were available from clinical trials pooled in the meta-analysis. It was not possible to make comparisons across other time periods because no reliable evidence was available on relative effectiveness for those time periods. For example, use of Norplant for 5 years relative to use of the contraceptive pill for 5 years was not included in the economic evaluation because a 5-year duration for these alternatives was not considered in a head-to-head trial included in the meta-analysis.

Measuring effectiveness

Effectiveness was measured in terms of pregnancies averted. Suppose we wish to measure the pregnancies averted by switching to contraceptive method A (a subdermal implant or IUS) from method B (some other contraceptive method). Pregnancies averted can be measured as the difference in pregnancy rates between the two methods, as follows:

$$\text{pregnancies averted} = PR_B - PR_A$$

where PR_B is the pregnancy rate with method B and PR_A is the pregnancy rate with method A. Estimation of effectiveness in this way requires data on the pregnancy rates for each contraceptive method compared.

Pregnancies averted were estimated in four stages.

1. Pregnancy rates for methods other than subdermal implants and IUSs were estimated for the UK population by the Steering Group members. These estimates were made with the assumption that the methods were used consistently and correctly for each specified time period. There is no standard used to estimate contraceptive failure rates in the UK population and most published estimates provide only 1-year failure rates. Estimates of contraceptive method failure rates are at best limited, and often flawed, because factors such as whether a method was used correctly and/or consistently or was used incorrectly and/or inconsistently are often not accounted for.[15,30]
2. Relative risks of pregnancy (pregnancy rate ratios) for subdermal implants and IUSs relative to other contraceptive methods were estimated directly from the meta-analysis using the quantitative synthesis methods explained above. Pregnancy rates of the other contraceptive methods, estimated as described in (1), were multiplied by the relative risk of pregnancy to calculate pregnancy rates for subdermal implants and IUSs. Although none of the studies included in the meta-analysis were based in the UK, the relative effectiveness calculated from the meta-analysis is likely to be stable across populations.
3. Pregnancy rates for subdermal implants and IUSs were subtracted from pregnancy rates for other contraceptive methods to calculate the attributable risk of pregnancy (pregnancy rate difference) for subdermal implants and IUSs relative to other contraceptive methods.
4. Two sensitivity analyses were conducted. The first used the lower and upper limits of the 95% CIs around the summary effect sizes for the pregnancy rate ratios. The second replaced the pregnancy rates estimated by the Steering Group with 'typical failure rates'* provided by Trussell and Kost.[15] These latter estimates were for pregnancy rates at 1 year only and estimates were not available for all of the contraceptive comparisons. For example there were no estimates for IUDs > 250 mm^3.

Measuring costs

All costs were calculated in 1998 UK£. Cost components included in the analysis were:

- net ingredient costs of contraceptive methods
- dispensing costs
- costs of FPC consultations (including consultations for fitting, monitoring and removing subdermal implants)
- expected costs of unplanned pregnancies.

Net ingredient costs were taken from the British National Formulary.[31] The cost of dispensing each contraceptive method was assumed to be £2. An FPC consultation was assumed to cost £31. It was assumed that four consultations are required for each contraceptive method in the first year and that one is required in each year following, where appropriate. Expected costs of unplanned pregnancies were based on the proportion of unplanned pregnancies that result in live births, induced abortions or spontaneous abortions. The probability that an unplanned pregnancy will result in one of these three endpoints was assumed to be 0.67, 0.23 and 0.1, respectively. The unit cost of these endpoints was assumed to be £1263, £362 and £289, respectively. Therefore, the average cost of an unplanned pregnancy was calculated to be £958 (i.e. [0.67 × £1263] + [0.23 × £362] + [0.1 × £289]). This average cost was then multiplied by the pregnancy rate associated with each contraceptive method to calculate the expected costs of unplanned pregnancies for that method.

* Trussell and Kost's explanation for the derivation of 'typical failure rates' is: "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." (reference 15, p. 271, Table 11).

Unit dispensing costs, number and unit costs of FPC consultations, and unit costs of live births, induced abortions and spontaneous abortions and their probabilities were taken (and updated where appropriate) from a previous comprehensive UK-based economic evaluation of contraceptive methods.[1]

Indirect costs were not included since the perspective of the analysis was the UK NHS. Hence the following were not included:

- indirect costs arising from time off work due to pregnancy
- indirect costs arising from income maintenance costs (i.e. child and parental financial support)
- indirect costs of adoptions arising from unplanned pregnancies.

Costs were measured as incremental costs of one alternative relative to another. Suppose we wish to measure the incremental costs of switching to contraceptive method A (a subdermal implant or IUS) from method B (some other contraceptive method). These can be measured as the difference in costs between the two methods, as follows:

$$\text{incremental costs} = (NIC_A + D + C_A + [PR_A \times P]) - (NIC_B + D + C_B + [PR_B \times P])$$

Where NIC_i is the net ingredient cost of method i (for i = A, B), D is the dispensing cost, C_i is the cost of FPC consultations for method i, PR_i is the pregnancy rate with method i and P is the average cost of an unplanned pregnancy.

Measuring cost-effectiveness

Cost-effectiveness is measured in terms of incremental costs per pregnancy averted. Suppose we wish to measure the cost-effectiveness of switching to contraceptive method A (a subdermal implant or IUS) from method B (some other contraceptive method). This can be measured as ratio of the incremental costs incurred by the change in method to the pregnancies averted, as follows:

incremental costs per pregnancy averted = incremental costs/no. of pregnancies averted

This calculates the additional cost of averting an extra pregnancy that arises from a switch to subdermal implants or IUSs from other contraceptive methods. Where cost-effectiveness is measured for a time period greater than 1 year, costs and outcomes are discounted to present values at an annual rate of 6%.

Chapter 3

Overview of search results

Nearly 6000 publications were identified through the search strategy. After the titles and/or abstracts had been read, 98 publications on subdermal implants and 72 publications on IUSs, which appeared to meet the inclusion criteria, were sought for review.

Despite attempts, it was not possible to locate two papers on subdermal implant papers[32,33] and three papers on IUSs.[34–36] Pre-publication copies of papers presenting the results of individual patient meta-analysis from trials comparing Implanon with Norplant were supplied by the manufacturer.[37–42] Unpublished data on Norplant were not released by the manufacturer. Unpublished data on the LNG-20 IUS from the study by Andersson and colleagues[43] was provided by the manufacturer (I Rauramo, Leiras Ltd: personal communication, 1999).

There was a low response rate to letters sent to study authors requesting further information. Those who responded could provide very little additional information or data.

Chapter 4

Results: subdermal implants

Characteristics of included studies

Overall, 34 comparative studies of contraceptive subdermal implants met the inclusion criteria. These included 15 RCTs identified from 22 publications and 19 non-randomised prospective cohorts identified from 22 publications. One study[44] comparing Norplant with Norplant-2 had initially randomised women to the different contraceptive methods, but randomisation was later temporarily suspended for 5 months because of a safety evaluation of the elastomer-382 contained in Norplant-2 implants. Therefore, for the review, this study was included with the non-randomised prospective cohort studies.

The characteristics of the studies are summarised in *Tables 2* and *3*. The majority (59%) of the 34 studies were conducted in developing countries, 29% were carried out in developed countries, and the remaining 12% were international multicentre studies. However, in terms of the number of women who were recruited, the RCT study population was nearly three times greater in developing countries than in developed countries (1771 women recruited in comparison with 656 women recruited, respectively), and the non-RCT prospective cohort study population was 12 times greater in developing countries (5405 women recruited in comparison with 459 women recruited, respectively).

The international multicentre RCTs, which were undertaken in both developed and developing countries, recruited 2349 women, making up 49% of the total number of women recruited in the studies included in this review. For the multicentre international RCTs it was difficult to ascertain whether the women were predominantly from developing or developed countries. None of the non-RCT cohort studies were international multicentre studies. The majority of studies were conducted in community settings (91%). In the three hospital studies,[62,65,81] the women were enrolled either after giving birth or after abortion in maternity units.

With the exception of two studies,[66,79] which limited recruitment to adolescent women, the majority of studies recruited women within a broad reproductive age range.

Information was collected from the papers on factors, other than the use of the contraceptive methods under investigation, which could potentially effect the fecundity of the study participants. Just over half of the studies stated that all of the women recruited had had a previous pregnancy or birth, thus ensuring the proven fertility of the population under investigation. In two studies breastfeeding women were recruited,[62,65] and the primary outcomes in these studies were the effects of subdermal implants on breastfeeding and infant growth. The Implanon studies[37] and five other studies[44,50,55,61,78] stated that the women recruited had to have a regular menstrual cycle.[47]

With one exception, a study in which Norplant-2 was compared with the LNG-20 IUS,[47] all of the RCTs compared two types of subdermal implant.

There was a much broader range of comparisons investigated in the non-randomised prospective cohorts (*Table 3*), although the methods that were compared with the subdermal implants were predominantly the more 'permanent' methods of contraception (i.e. methods that would require women to actively seek medical attention to discontinue). However, there were studies comparing implants with methods such as, for example, the contraceptive pill. In general, the populations recruited into these studies were younger.[66,69]

Only five of the non-randomised studies stated that the intervention groups had similar characteristics at entry to the study.[44,68,73,75,81] In *Table 3* differences between the intervention groups at study entry are shown if the study authors stated that there was a statistically significant between the intervention groups for a demographic or clinical characteristic. In general, in comparison with women using other methods of contraception, the women using subdermal implants tended to be older, have had more pregnancies, have had more children, and have lower levels of education, and were more likely to have previously tried another method of contraception.

Information was collected on factors that could potentially effect the results of studies. These effect modifiers included whether or not women

TABLE 2 *Characteristics of included studies on subdermal implants: RCTs*

Study*†	Setting	Description of participants	No. randomised	Intervention (no. randomised)	Primary outcomes	Length of follow-up
Implanon studies	International multicentre	Age: 18–40 years Regular menses	See below Total = 1578	Implanon vs. Norplant	Pregnancy Menstrual disturbance Hormonal side-effects Adverse events Insertions and removals Ovarian function	See below
Croxatto & Makarainen, 1998[37]	Finland (Study 34508)	As above	32	Implanon (*n* = 16) Norplant (*n* = 16)		3 years
Affandi, 1998[38]	Finland and Sweden (Study 34509)	As above	86	Implanon (*n* = 43) Norplant (*n* = 43)		2 years
Urbancsek, 1998[39]	Indonesia and Thailand (Study 34510)	As above	120	Implanon (*n* = 60) Norplant (*n* = 60)		3 years
Mascarenhas, 1998[41]	Singapore (Study 34511)	As above	80	Implanon (*n* = 40) Norplant (*n* = 40)		2 years
Makarainen, *et al.*, 1998[42]	Finland and Indonesia (Study 34512)	As above	161	Implanon (*n* = 81) Norplant (*n* = 80)		2 years
	Indonesia (Study 34520)	As above	899	Implanon (*n* = 449) Norplant (*n* = 500)		3 years
	China (Study RM04)	As above	200	Implanon (*n* = 100) Norplant (*n* = 100)		4 years
Sivin, *et al.*, 1997a[45] Sivin, *et al.*, 1997b[46]	International multicentre	Age: 18–40 years Variable parity (< 2 births on average) Weight: 50–60 kg (mean)	1198	LNG-rods (*n* = 600) Norplant-2 rods (*n* = 598)	Pregnancy Continuation Reasons for discontinuation Serum LNG levels	3 years
***Wang, *et al.*, 1992**[47] Gao, *et al.*, 1990[48] Wang, 1990[49]	China FPCs	Age: 20–40 years Parous Not breastfeeding	200	Norplant-2 (*n* = 100) LNG-20 IUS (*n* = 100)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	3 years
Darney, *et al.*, 1992[50] Darney, *et al.*, 1989[51]	USA FPCs	Age: 18–35 years Parous Regular menses	48	Capronor implants: 2.5-cm capsules (12 mg LNG) (*n* = 16) 4-cm capsules (21.6 mg LNG) (*n* = 16)	Serum LNG levels	1 year
***Olsson, *et al.*, 1988**[52] Olsson, 1987a[53] Olsson, *et al.*, 1987b[54]	Sweden	Age: 18–40 years Parous	240	Norplant (*n* = 69) Norplant-2 (*n* = 171)	Pregnancy Continuation Reasons for discontinuation Plasma LNG levels	3 years
***Pasquale, *et al.*, 1987**[55]	USA	Age: 18–40 years Parous Not breastfeeding	250	Norplant (*n* = 75) Norplant-2 (*n* = 175)	Pregnancy Continuation Reasons for discontinuation	3 years

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

TABLE 2 contd *Characteristics of included studies on subdermal implants: RCTs*

Study*†	Setting	Description of participants	No. randomised	Intervention (no. randomised)	Primary outcomes	Length of follow-up
***Hingorani, et al., 1986**[56]	India Human Reproductive Research Centres	Age: 18–35 years Parous Not breastfeeding Regular menses	172	Norplant (*n* = 84) Norplant-2 (*n* = 88)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	2 years
Nielsen, et al., 1979[57] Coutinho, *et al.*, 1978[58] Coutinho, *et al.*, 1978[59] Faundes, *et al.*, 1978[60]	International multicentre (Brazil, Chile, Dominican Republic, Jamaica and Scandinavia)	Age: 18–35 years Parous Not breastfeeding	990	Norplant implant (*n* = 492) R2010 (norgestrienone) implant (*n* = 498)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance Hormonal side-effects	1 year
Alvarez, et al., 1978[61]	Dominican Republic	Age: 17–44 years Variable parity Not breastfeeding Regular menses	100	LNG implant (*n* = 52) R2323 implant (*n* = 48)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance Hormonal side-effects	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

had received contraceptive counselling before starting the method, whether the healthcare worker who inserted the subdermal implants had received specialist training, and whether the appropriate date of insertion was documented. It was not applicable to collect this information in three studies in which the outcome of interest was pregnancy after discontinuation of method.[72,75,76] In the remaining 30 studies, eight reported whether or not the women were counselled,[44,47,63,66,68,70,79,82] 16 provided information on insertion dates,[37,47,52,55,56,62,65,68,77,81] and three stated that insertions were conducted by professionals who had received some training on implant insertion.[47,77,82]

Information on insertion date was more frequently reported for RCTs than for non-RCT comparisons (73%[37,47,52,55,56] versus 31%[62,65,68,77,81]), but RCTs were less likely than non-RCTs to state whether the women had received counselling (7%[47] versus 50%[44,62,66,68,70,79,80,82]). None of the RCTs stated whether or not the healthcare professionals had received specialist training.

Excluded studies

Twenty-six studies (29 publications) were excluded (see appendix 5). Two papers[40,84] were excluded (one did not report any outcomes relevant to the review and the other did not report the results of the investigated interventions separately) but other publications of the same studies were included. The most common reason for exclusion was that studies did not report any outcomes that had been identified in the protocol (35%), followed by inappropriate study design (31%), which had not been identified by the initial reading of the abstract (i.e. the studies were not prospective comparative interventions).

Quality

The quality of each publication was assessed independently by the two reviewers (RF and FC). Two publications[49,57] were assessed by RF working with a translator. The reviewers were blinded to both source and authors. Complete initial inter-reviewer agreement on all quality assessment factors for each study was 40% (17/42). Initial agreement was higher for RCT studies than for non-randomised cohort studies – 50% (10/20) compared with 32% for the non-randomised cohort studies (7/22). When assessment was based on factors related to study design, such as allocation concealment and blinded assessment of outcomes, inter-reviewer agreement was much higher. Lower inter-reviewer agreement was found on the specific contraceptive methodological factors, such as the method of life-table analysis reported. All of the reviewer differences in initial

TABLE 3 *Characteristics of included studies on subdermal implants: non-randomised prospective cohort studies*

Study*†	Setting	Description of participants	No. enrolled	Intervention (no. per group)	Primary outcomes	Group comparability at entry	Length of follow-up
***Del Carmen Cravioto, et al., 1997[44]**	Mexico 8 FPCs	Age: 18–40 years Parous Not breastfeeding Regular menses	1052	Norplant (*n* = 533) Norplant-2 (*n* = 519)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance User satisfaction	Similar at entry	3 years
***Diaz, et al., 1997[62]**	Chile Maternity unit	Age: 18–38 years Parity: 1–3 Previous normal pregnancy Breastfeeding	546	Norplant (*n* = 120) Progesterone vaginal rings (*n* = 187) Progestin oral contraceptive (*n* = 117) CuT 380A IUD (*n* = 122)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance Effect on breastfeeding Infant growth	CuT 380Ag IUD users older than women using the other methods	1 year
Noerpramana, 1997[63]	Indonesia Hospital and Primary Health Care Centre	Age: 20–40 years Not breastfeeding	180	Norplant (*n* = 91) Non-hormonal IUD (*n* = 89)	Blood-lipin fractions	Norplant users younger and had lower occupation status	2 years
***Singh & Ratnam, 1997a[64]**	Singapore	Age: 25–40 years Parous Not breastfeeding Regular menses	80	Norplant (*n* = 40) CuT 380 IUD (*n* = 40)	Pregnancy Continuation Reasons for discontinuation Pregnancy after discontinuation of method	Norplant users younger and had lower ponderal index	5 years
***Abdel Aleem, et al., 1996[65]**	Egypt Dept of Obstetrics and Gynaecology (hospital)	*Post partum* (2nd month) Breastfeeding	240	Uniplant (*n* = 120) CuT 380A IUD (*n* = 120)	Pregnancy Breastfeeding performance Infant growth	Uniplant users had more previous pregnancies, had more living children, were more likely to live in a rural area and were more likely to be illiterate	1 year
Hollander, 1995[66] Polaneczky, *et al.*, 1994[67]	USA FPCs	Age: ≤ 17 years *Post partum*	98	Norplant (*n* = 48) Oral contraceptives (*n* = 50) Both groups encouraged to use condoms	Pregnancy Continuation (incl. condom use) Sexually transmitted diseases User satisfaction	Norplant users older, more likely to have been pregnant and given birth ≥ 2 times, and more likely to have had previous contraceptive experience	20 months
Mainwaring, et al., 1995[68]	USA Dept of Obstetrics and Gynaecology	Age: 16–43 years	71	Norplant (*n* = 44) DMPA injections (*n* = 22) Oral norethindrone (*n* = 25)	Metabolic parameters Menstrual disturbance	Similar at entry	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

continued

TABLE 3 contd *Characteristics of included studies on subdermal implants: non-randomised prospective cohort studies*

Study*†	Setting	Description of participants	No. enrolled	Intervention (no. per group)	Primary outcomes	Group comparability at entry	Length of follow-up
***Cromer, *et al.*, 1994[69]**	USA General Adolescent Health Clinic	Age: 11–20 years Various parity	199	Norplant (*n* = 58) DMPA injections (*n* = 68) Combined oral contraceptive pill (*n* = 75)	Continuation Menstrual disturbance Hormonal side-effects User satisfaction	Norplant and DMPA users more likely to have been pregnant and have had problems with oral contraceptives. DMPA users more likely to have been on previous contraception and to have had a sexually transmitted infection	6 months
***Fakeye, 1992[70]**	Nigeria FPCs	Age: 18–40 years	210	Norplant (*n* = 80) Low-dose oral contraceptive pill (*n* = 130)	Body weight Blood pressure	Norplant users older, had more children and had more years of formal education	1 year
Fakeye, 1991[71]			357	Norplant (*n* = 50) Oral contraceptive pill (*n* = 101) DMPA injections (*n* = 22) Various non-hormonal IUDs (*n* = 184)	Pregnancy Continuation Reasons for discontinuation	Norplant users older than pill and IUD users. Norplant users had greater mean number of children than pill users, but lower mean number than DMPA users. Norplant users had higher level of education compared with all other groups.	
***Sivin, *et al.*, 1992[72]**	International FPCs	Mean age: 27.8 years Cohort from RCTs discontinuing contraception to become pregnant Variable parity	372	Norplant (*n* = 62) Norplant-2 (*n* = 116) (See Olsson, *et al.*, 1988[52]) LNG-IUS (20 µg/day) (*n* = 91) CuT 380Ag IUD (*n* = 103) (See Sivin & Stern, 1994[73])	Pregnancy after discontinuation of method	Norplant users older than Norplant-2 users and had been using method for a shorter time than CuT 380Ag IUD users	2 years
***Singh, *et al.*, 1990[74]**	Singapore Fertility Control Clinic	Age: 18–40 years Parous Not breastfeeding	200	Norplant (*n* = 100) Norplant-2 (*n* = 100)	Pregnancy Continuation Reasons for discontinuation Hormonal side-effects	Similar at entry	2 years
***Affandi, *et al.*, 1987[75]**	Indonesia Dept of Obstetrics and Gynaecology	Age: 20–34 years Parous Use of contraceptive method for ≥ 12 months Wishing to become pregnant	173	Norplant (*n* = 51) Lippes C IUD (*n* = 75) DMPA injections (*n* = 47)	Pregnancy after discontinuation of method	Similar at entry	2 years

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

continued

TABLE 3 contd *Characteristics of included studies on subdermal implants: non-randomised prospective cohort studies*

Study*†	Setting	Description of participants	No. enrolled	Intervention (no. per group)	Primary outcomes	Group comparability at entry	Length of follow-up
*Diaz, *et al.*, 1987[76]	Chile	Mean ± SD age: Norplant, 29.7 ± 5; CuT IUD, 28.4 ± 4 Proven fertility Wishing to become pregnant	134	Norplant (*n* = 90) CuT IUD (*n* = 44)	Pregnancy after discontinuation of method	Not stated	2 years
Lopez, *et al.*, 1986[77]	Columbia FPCs	Age: 15–40 years Proven fertility	493	Norplant (*n* = 389) CuT 380Ag IUD (*n* = 104)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	Enrolment of IUD users predominantly confined to one clinic	1 year
*Roy, *et al.*, 1984[78]	USA Dept of Obstetrics and Gynaecology	Age: 18–35 years Parous Regular menses	23	Norplant (*n* = 11) Norplant-2 (*n* = 12)	Serum LNG levels Menstrual disturbance Hormonal side-effects	Unclear	2 years
Shaaban & Salah, 1984[79] Shaaban, *et al.*, 1983[80]	Egypt FPCs	Age: 25–40 years Parous	350	Norplant (*n* = 250) CuT 380Ag IUD (*n* = 100)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance Hormonal side-effects	Norplant users had more children, were more likely not to want more children and had higher illiteracy	2 years
*Kurunmaki, 1983[81]	Finland Hospital	After abortion	68	Norplant (*n* = 38) Nova-T IUD (*n* = 30)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance Hormonal side-effects	Similar at entry	1 year
*Marangoni, *et al.*, 1983[82]	Ecuador 2 FPCs	Parous	566	Norplant (*n* = 283) CuT 200 IUD (*n* = 283)	Pregnancy Continuation Reasons for discontinuation	Norplant users younger	1 year
Croxatto, *et al.*, 1975[83]	Chile 3 medical centres		824	Various implants: MA with 5 and 6 capsules d-Ng with 3 and 4 capsules Norethindrone MA with 4 capsules plus d-Ng with 1 capsule MA with 4 capsules plus d-Ng with 2 capsules	Pregnancy Menstrual disturbance Unplanned pregnancy outcomes Pregnancy after discontinuation of method	Not stated	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

MA, Megestrol acetate; d-Ng, d-norgestrel

assessment were resolved after discussion and it was not necessary to ask the advice of a third party.

A breakdown of methodological factors that could impact on study results is shown in appendix 6.

RCTs

For three of the 15 RCTs the method of randomisation was described by the authors.[45,47,52] Allocation concealment was described in five of the trials[45,47,52,55,57] and the investigators were blind at follow-up assessments to allocated contraceptive methods in only one of the trials.[57]

For 13 of the trials, the authors clearly stated that the intervention groups were treated identically.[37,45,47,52,55–57] None of the included studies provided any information on women who withdrew or who were lost to follow-up, and so it was impossible to determine whether or not the characteristics of these women were similar to those of women who remained in the study.

Excluding the meta-analyses data of the seven Implanon studies,[37] in which the investigators pooled PIs to provide summary effect sizes for pregnancy and discontinuation, six of the remaining eight studies used life-table analysis to report probabilities for these outcomes.[45,47,52,56,57,61] Five studies provided single decrement life-table probabilities.[45,47,52,56,57] For one of the studies,[61] it was not possible to determine whether or not single or multiple decrement life tables had been calculated to report results.

Seven of the 15 included studies provided a description of the contraceptive methods women were using before enrolment.[45,47,50,52,55,57,61] Although user failure is unlikely to be a factor in comparisons of two types of subdermal implants, five of the six studies reporting pregnancies[47,50,52,55,57] gave details about the possible causes of pregnancy, for example a woman being pregnant before the implant was inserted. Active follow-up analysis was conducted in two of the 15 studies.[45,57]

Non-randomised prospective cohort studies

In 14 of the 19 cohort studies, the invention groups were treated identically in terms of investigations and follow-up visits.[62–66,72,69,70,74,76,78,80–82] There was only one trial[65] in which the investigators were blind to allocated contraceptive method when assessing outcomes at follow-up.

Similar rates of follow-up between intervention groups were reported in 13 studies.[44,62–66,69,72,74,76,78,82] None of the studies provided any demographic details about those women who withdrew from the study or were lost to follow-up. Two studies did report a 100% follow-up rate.[63,78]

A few of the studies restricted entry to certain population groups (i.e. to adolescents or women *post partum*; see 'Characteristics of included studies' page 13). Only one of the studies controlled for confounding through matching: Roy and colleagues[78] matched women by ponderal index at entry.

Of the 17 studies reporting pregnancy and continuation outcomes, ten used life-table analysis,[44,64–66,72,74,76,77,79,82] one used PIs[83] and the remaining six used other methods. In only two studies was it possible to determine whether single or multiple decrement life tables had been used.[76,77] Both of these studies did report single decrement probabilities.

Ten of the 19 studies provided a description of contraceptive methods before enrolment.[44,62,64,66,74,77–79,82,83] In the ten studies reporting pregnancy outcomes,[44,62,64,66,74,77–79,82,83] six provided sufficient information to distinguish between user and method failure.[44,64,66,74,79,83] None of the studies conducted active follow-up analysis.

Quality differences between the RCTS and non-RCTs

Other than the obvious differences in study design, there was little difference between the RCTs and non-RCTs with respect to the assessed quality factors. The only significant difference was that RCTs were more likely to use single decrement life-table probabilities to report unwanted pregnancies and continuation of contraceptive method.

Quantitative synthesis of studies

Data from 18 of the 34 studies that met the inclusion criteria were included in the meta-analysis. Five studies were excluded from the meta-analysis because they were investigations of prototypes[45,50,57,61,83] and it was deemed inappropriate to pool their data. We were unable to determine the types of IUDs used as the controls in one study[63] and it was not possible to extract any data from the remaining studies,[66,68,77] as neither single decrement life-table probabilities with SEs nor events over time were reported. It was not possible to extract data from the meta-analysis of the seven

Implanon versus Norplant trials, as the number of events for each separate trial could not be determined even though the number of women cycles was reported for each trial.[37]

Meta-analysis

The studies included in the meta-analysis are marked with asterisks in *Tables 2* and *3*.

Norplant

Excluding the meta-analysis of the seven Implanon versus Norplant trials, there were 16 comparative studies with Norplant included in the meta-analysis, of which three were RCTs.[52,55,56] The most common comparison was Norplant versus Norplant-2 (six studies[44,52,55,56,74,78]), followed by Norplant versus CuT 380Ag IUDs (four studies[62,72,77,79]).

Pregnancy

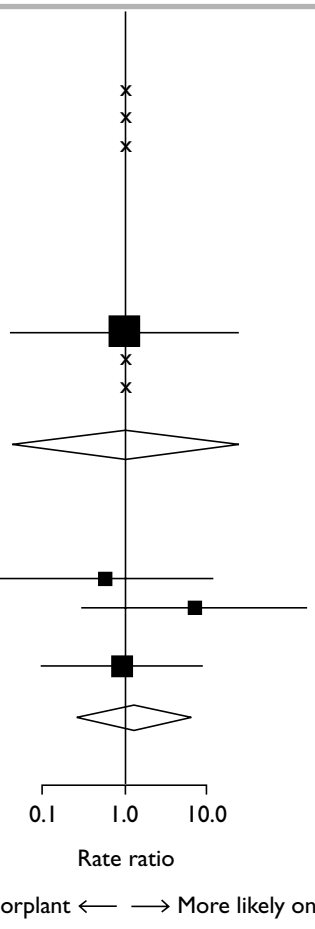
Table 4 shows that the contraceptive effects of Norplant and Norplant-2 were similar over a 3-year period. This was also reflected by the single decrement life-table probability difference calculated from one study at year 3 follow-up.[52] The rate was zero in the Norplant group and 2.1 (SE, ± 1.5) in the Norplant-2 group, giving an absolute difference of –2.1% (95% CI, –6.26% to 2.06%).

In the seven trials of Implanon versus Norplant,[37] over 21,018 and 21,983 women months of follow-up, respectively, there were no pregnancies in either of the intervention groups.

There was some indication that over 1 and 2 years of follow-up, Norplant users were less likely to become pregnant than were users of the other reversible methods of contraception, in

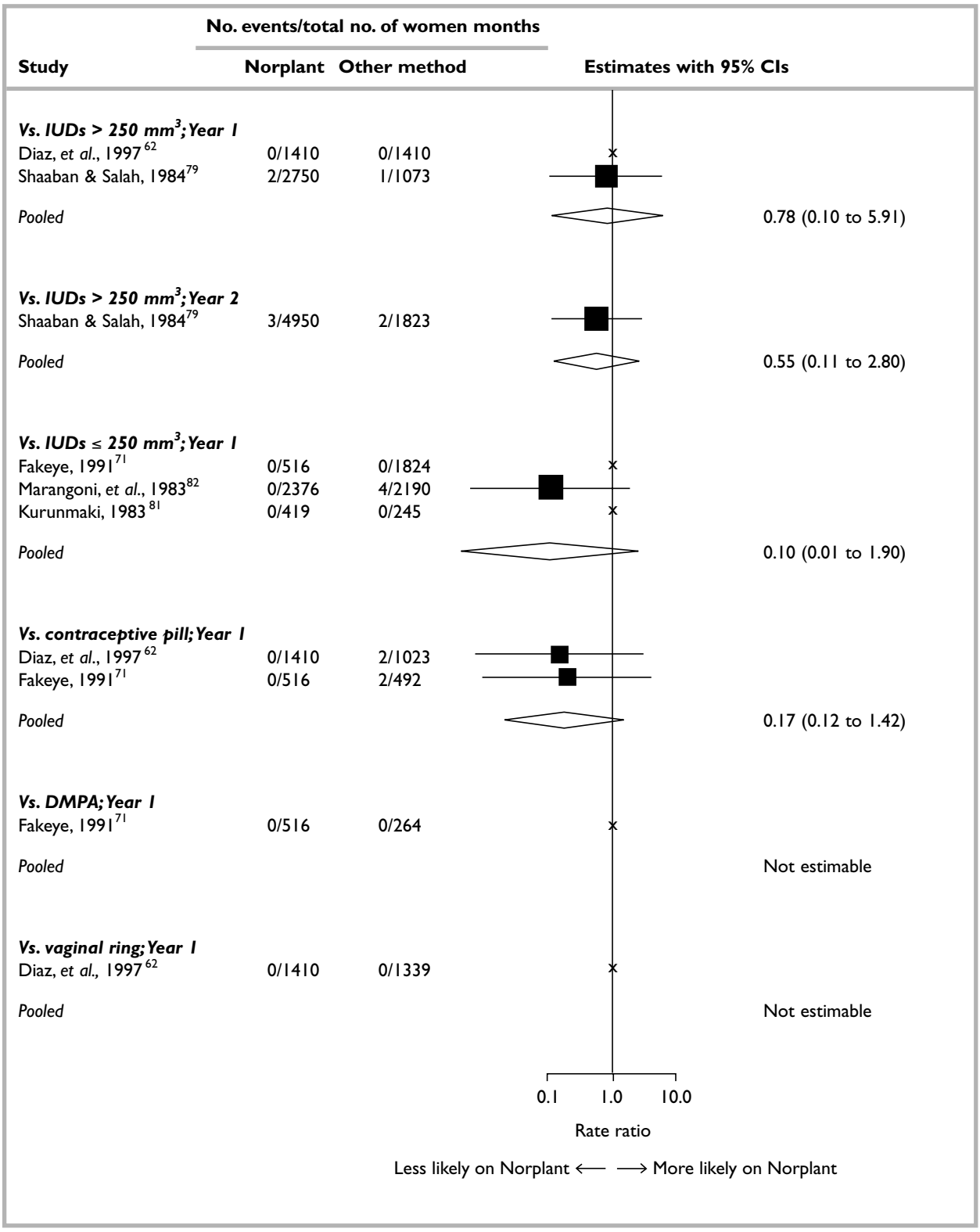
TABLE 4 *Pregnancy: Norplant compared with Norplant-2*

Study	No. events/total no. of women months: Norplant	Norplant-2	Estimates with 95% CIs
Year 1			
Olsson, *et al.*, 1988[52]	0/681	0/1816	
Hingorani, *et al.*, 1986[56]	0/981	0/897	
Roy, *et al.*, 1984[78]	0/130	0/128	
Pooled			Not estimable
Year 2			
Olsson, *et al.*, 1988[52]	0/1108	1/3163	
Hingorani, *et al.*, 1986[56]	0/1777	0/1590	
Roy, *et al.*, 1984[78]	0/250	0/218	
Pooled			0.95 (0.04 to 23.36)
Year 3			
Olsson, *et al.*, 1988[52]	0/1473	2/4164	
Pasquale, *et al.*, 1987[55]	1/1335	0/3129	
Del Carmen Cravioto, *et al.*, 1997[44]	1/15,279	1/14,092	
Pooled			1.32 (0.27 to 6.42)



particular users of the oral contraceptive pill or the CuT ≤ 250 mm^3 IUD (see *Table 5*), although the findings were not statistically significant. There was evidence of heterogeneity of the results between the studies of Norplant versus the oral contraceptive pill at year 1. Data from the Hollander study,[66] which could not be synthesised, showed that pill users were significantly more likely to become pregnant than Norplant users: 19 of the 48 pill users became pregnant over the follow-up period, in comparison with one of the 50 Norplant users.

TABLE 5 *Pregnancy: Norplant compared with other methods*



Continuation of method

There was no difference in the continuation rates over time between Norplant and Norplant-2 users (*Table 6*). The difference in continuation rates was not affected by whether or not women had been initially randomised to the studies.

There were significant differences in continuation rates when Norplant was compared with some of the other contraceptive methods (*Table 7*). At 1 year, Norplant users were nearly twice as likely to continue with the method when compared with pill users (rate ratio, 1.9; 95% CI, 1.4 to 2.5), or with women using vaginal rings (rate ratio, 1.8; 95% CI, 1.3 to 2.4). At 1 year, Norplant users were nearly two and a half times more likely to continue with the method than women having depomedroxyprogesterone acetate (DMPA) injections (rate ratio, 2.4; 95% CI, 1.2 to 4.6). One non-RCT study comparing Norplant users with IUD ≤ 250 mm^3 users[82] provided single decrement life-table probabilities and no difference in continuation of method was found (–0.5%; 95% CI, –7.15% to 6.15%).

Rate of pregnancy after removal

The data extracted to determine the risk ratio for pregnancy after discontinuation of contraceptive method suggested no significant difference between Norplant and the other methods used as a comparison. All of the women had initially discontinued the method because they were planning a pregnancy. The numbers of women followed up in these studies were small. The risk of pregnancy after discontinuation when Norplant was compared with Norplant-2 at 1 year of follow-up was 1.65 (95% CI, 0.9 to 2.9),[74] with nine out of ten women who had used Norplant becoming pregnant in comparison with six of the 11 women who had used Norplant-2.

TABLE 6 *Continuation: Norplant compared with Norplant-2*

Study	No. events/total no. of women months: Norplant	Norplant-2	Estimates with 95% CIs
Year 1			
Olsson, *et al.*, 1988[52]	41/681	132/1816	
Hingorani, *et al.*, 1986[56]	82/981	76/897	
Pooled			0.91 (0.72 to 1.15)
Year 2			
Olsson, *et al.*, 1988[52]	32/1108	98/3163	
Hingorani, *et al.*, 1986[56]	68/1777	60/1590	
Roy, *et al.*, 1984[78]	10/250	7/218	
Pooled			0.99 (0.77 to 1.28)
Year 3			
Pasquale, *et al.*, 1987[55]	56/1335	140/3129	
Del Carmen Cravioto, *et al.*, 1997[44]	264/15,279	258/14,092	
Pooled			0.94 (0.81 to 1.09)

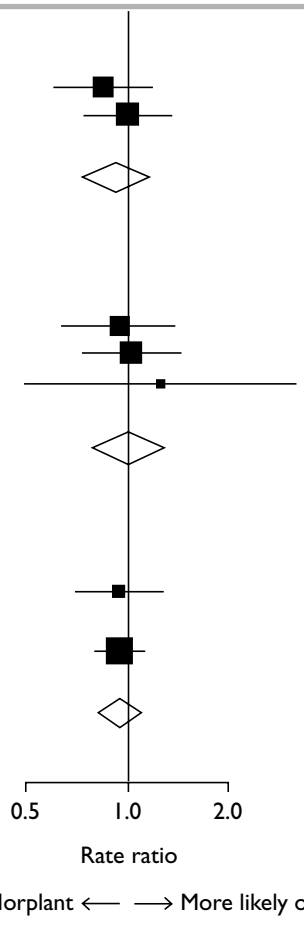
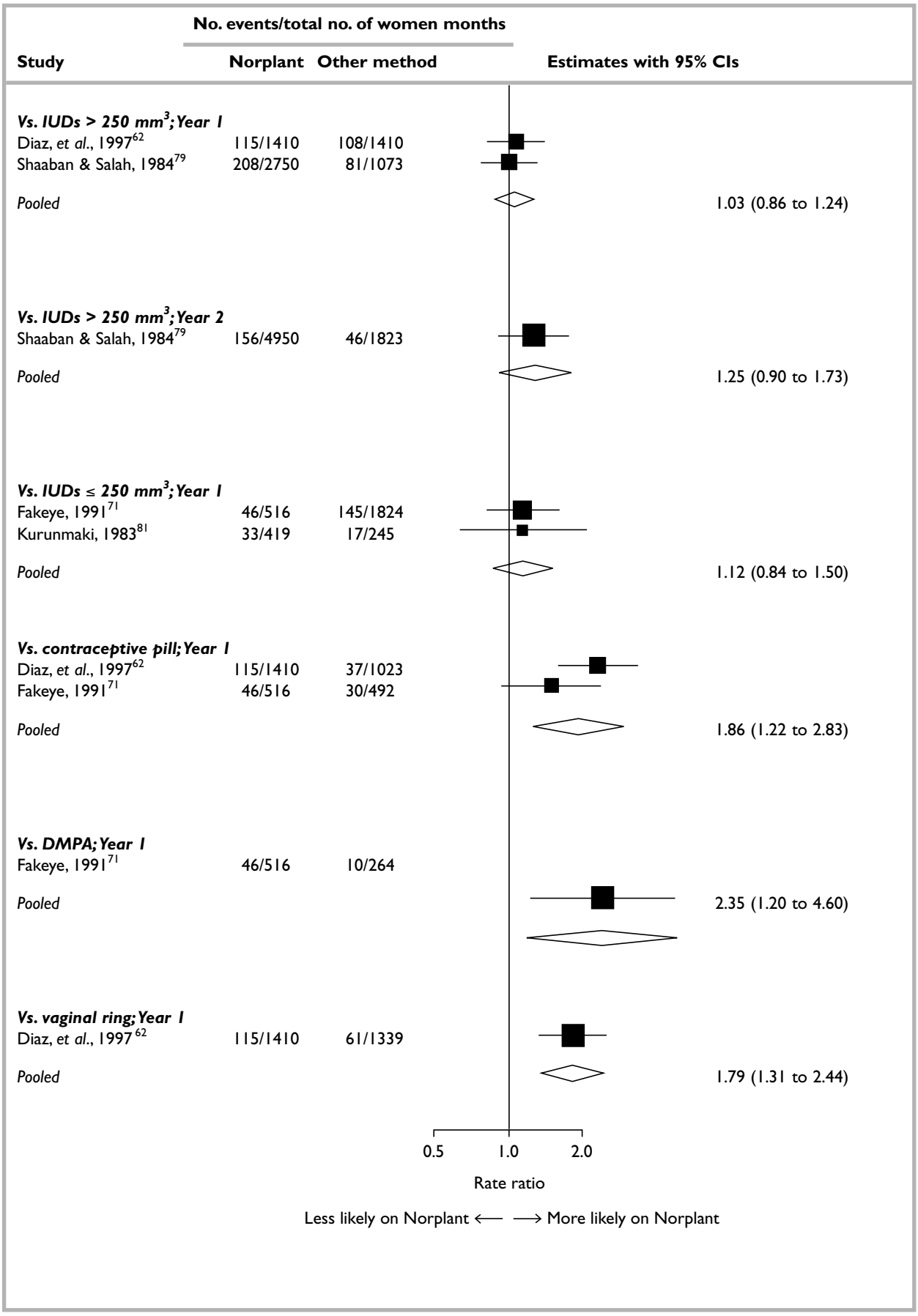


TABLE 7 *Continuation: Norplant compared with other methods*



When ex-Norplant users were compared with ex-IUD users, the risk of pregnancy was 1.05 (95% CI, 0.56 to 1.96) at 1 year (11/14 ex-Norplant users became pregnant in comparison with three out of four ex-IUD users).[64] At 2 years, the risk of pregnancy was 0.96 (95% CI, 0.92 to 1.01) (75/78 ex-Norplant users became pregnant in comparison with 38/38 ex-IUD users).[76]

Nor was a significant difference noticed when ex-Norplant users were compared with women who had had DMPA injections. Of 51 ex-Norplant users, 39 had become pregnant at year 1 and 46 had become pregnant at year 2. Of 47 ex-DMPA users, 33 had become pregnant at year 1 and 42 had become pregnant at year 2. These numbers give risk ratios for pregnancy after discontinuation (Norplant versus DMPA injections) of 1.09 (95% CI, 0.86 to 1.39) and 1.01 (95% CI, 0.88 to 1.15) at 1 and 2 years, respectively.[75]

All of these risk ratios were calculated from individual studies.

Hormonal side-effects

Although hormonal side-effects were reported in some studies, it was only possible to calculate risk ratios from one study that compared Norplant with Norplant-2. This was the only study that reported the number of hormonal side-effect events and the number of women at follow-up.[74] The 2-year follow-up data collected from this study, and the calculated risk ratios, are summarised in *Table 8*.

The results reported in the study by Cromer and colleagues[69] showed no significant differences between users of Norplant, DMPA and the pill with regards the following side-effects: headaches, nausea, dizziness, depression, acne and weight gain. It was not possible to include these data in the meta-analyses.

Olsson and colleagues[52] were the only investigators to supply sufficient information to calculate mean difference in weight gain. In their study, mean weight gain was greater among Norplant users than among Norplant-2 users, with differences of 0.4 kg (95% CI, –0.91 kg to 1.71 kg) at year 1, 2.9 kg (95% CI, 0.26 kg to 5.54 kg) at year 2, and 0.8 kg (95% CI, –1.75 kg to 3.35 kg) at year 3.

It was not possible to collect any data for the following outcomes, which had been identified in the protocol: pelvic pain, hair growth, ovarian cysts, uterine cramps and mood changes.

Menstrual disturbance

Two studies provided data on menstrual disturbance that could be extracted and the results are summarised in *Table 9*. There are very wide CIs around many of the risk ratios when there were no events in one of the comparison groups.

In general, over the 90-day intervals, women using Norplant were significantly less likely to experience dysmenorrhoea, spotting, menorrhagia and prolonged bleeding than were the women using IUDs > 250 mm^3.

Women using Norplant were significantly more likely to experience amenorrhoea than were women using IUDs > 250 mm^3 or the oral contraceptive pill, although with the latter comparison the significance was lost by 6 months follow-up. No significant difference was noticed when women using Norplant were compared with women having DMPA injections, although data from the study by Mainwaring and colleagues,[68] which was not included in the meta-analysis, indicated that women having DMPA injections were significantly more likely to experience amenorrhoea than were Norplant users. This latter study also reported that Norplant users were significantly more likely

TABLE 8 *Risk of hormonal side-effects in subdermal implant users*

	No. of events		
Side-effect	**Norplant (*n* = 79)**	**Norplant-2 (*n* = 78)**	**Risk ratio (95% CI)**
Headaches	0	3	0.14 (0.01 to 2.75)
Acne	0	0	–
Breast tenderness	0	2	0.2 (0.01 to 4.14)
Nausea	0	0	–
Dizziness	0	0	–
Hair loss	0	1	0.34 (0.01 to 8.13)
Loss of libido	0	0	–

TABLE 9 *Risk ratios for menstrual disturbance in Norplant users relative to users of other contraceptive methods*

	Risk ratio (95% CI)					
Follow-up period	**Dysmenorrhoea**	**Spotting**	**Oligomenorrhoea**	**Amenorrhoea**	**Menorrhagia**	**Prolonged bleeding**
Norplant vs. CuT 380Ag IUD*						
1–90 days	0.03 (0.002 to 0.45)	0.09 (0.03 to 0.26)	–	68.28 (4.23 to 1102.53)	0.25 (0.13 to 0.51)	0.17 (0.06 to 0.49)
91–180 days	0.03 (0.002 to 0.45)	0.49 (0.23 to 1.05)	–	19.52 (2.68 to 142.2)	0.28 (0.14 to 0.59)	0.18 (0.06 to 0.58)
181–270 days	0.03 (0.004 to 0.20)	0.31 (0.13 to 0.76)	–	28.68 (1.73 to 475.37)	0.58 (0.29 to 1.17)	0.67 (0.06 to 0.58)
271–360 days	0.03 (0.003 to 0.20)	0.81 (0.32 to 2.10)	–	12.85 (1.73 to 475.37)	0.37 (0.16 to 0.84)	0.23 (0.07 to 0.77)
2 years	–	–	8.81 (0.48 to 160.75)	34.27 (2.12 to 554.8)	0.58 (0.23 to 1.29)	0.2 (0.03 to 1.14)
Norplant vs. DMPA injections†						
1–90 days	–	–	–	0.85 (0.41 to 1.76)	–	–
91–180 days	–	–	–	0.6 (0.25 to 1.41)	–	–
Norplant vs. oral contraceptive pill†						
1–90 days	–	–	–	20.19 (1.24 to 328.5)	–	–
91–180 days	–	–	–	3.43 (0.44 to 26.67)	–	–

* *Data from Shaaban & Salah, 1984*[79]
† *Data from Cromer,* et al., *1974*[69]

to experience prolonged menstrual bleeding than were women having the DMPA injections.

Local device problems

None of the studies provided information on implant insertion and removal times, with the exception of the paper by Mascarenhas[41] which was part of a series of meta-analyses of Implanon versus Norplant. Procedure times were available for 670 women having Implanon inserted and for 665 women having Norplant inserted. The mean insertion time was 1.1 minutes (SD, 0.9; range 0.03 to 5 minutes) for Implanon, and 4.3 minutes (SD, 2.1; range, 0.83 to 18 minutes) for Norplant. Removal times were available for 633 Implanon users and 137 Norplant users. The mean removal time was 2.6 minutes (SD, 2.0; range, 0.02 to 20 minutes) for Implanon and 1.3 minutes (SD, 8.2; range, 1.3 to 50 minutes) for Norplant.

Failed implant removal. None of the studies reported any failed implant removals. The Mascarenhas paper[41] reports that Norplant users were significantly more likely than Implanon users to experience problems at removal, although the number of problematic removals was small. The most common problem with Norplant removals was broken capsules.

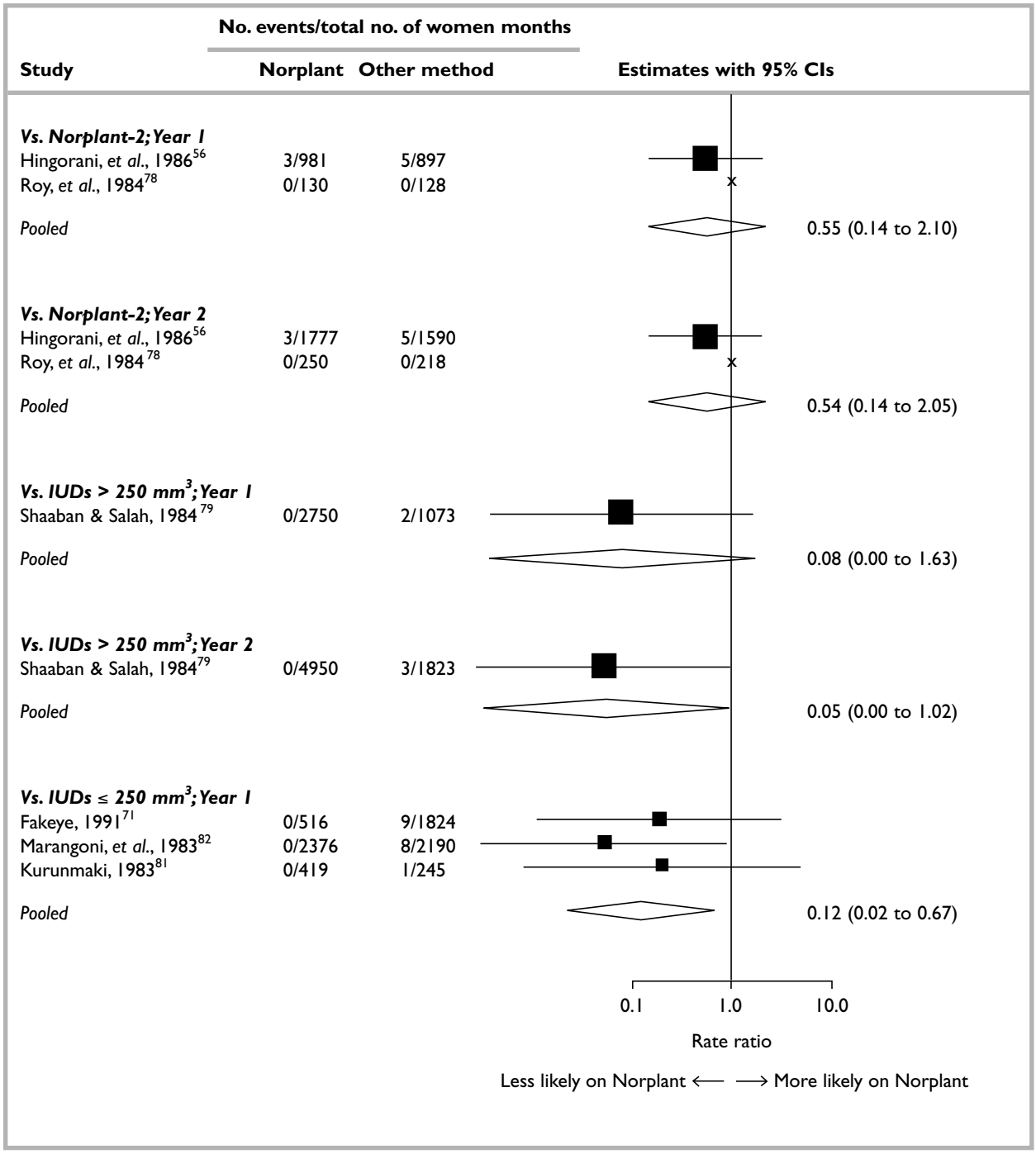
Local sepsis. Only one study[78] provided any information on local sepsis. No local sepsis events were reported after 250 and 218 women months of use, respectively.

Expulsion. The summary effect rate ratio sizes for expulsion are shown in *Table 10*. The difference in expulsion rates was significant only for the Norplant versus IUD ≤ 250 mm^3 comparison (0.12; 95% CI, 0.02 to 0.7). One RCT[56] comparing Norplant with Norplant-2 provided single decrement life-table probabilities and no significant difference was found. The probabilities at years 1 and 2 were 3.5 (SE, ± 2.0) and 6.1 (SE, ± 2.6) for Norplant and Norplant-2, respectively, giving an absolute difference of –2.6% (95% CI, –9.03% to 3.83%).

Adverse clinical events

Olsson and colleagues[52] reported that there were no ectopic pregnancies in the Norplant group after 681 women months of follow-up and that there was one ectopic pregnancy in the Norplant-2 group after 1816 women months

TABLE 10 *Expulsion: Norplant compared with other methods*



of follow-up, giving a rate ratio of 0.89 (95% CI, 0.03 to 21.8).

Del Carmen Cravioto and colleagues,[44] in their investigation of Norplant compared with Norplant-2, reported that at 3 years follow-up (15,279 women months and 14,092 women months for Norplant and Norplant-2, respectively), there had been one diagnosis of breast cancer in the Norplant-2 group (rate ratio 0.3; 95% CI, 0.01 to 7.58), and no diagnosis of cervical neoplasia III in either group. One woman in the Norplant group and two women in the Norplant-2 group died. The deaths were unrelated to the methods of contraception.

No deaths were reported in the Implanon versus Norplant trials.[37]

No further data on other adverse events identified in the protocol were extracted from the included studies.

Reasons for discontinuation

Hormonal side-effects. *Table 11* shows the studies included in the meta-analysis that provided data on hormonal side-effects as a reason of discontinuation of a contraceptive method. There was no evidence to suggest that women using Norplant were any more or less likely to discontinue for this reason than were Norplant-2 or IUD ≤ 250 mm^3 users.

Menstrual disturbance. When studies in which any menstrual disturbance was given as a reason for women discontinuing a contraceptive method were combined (see *Tables 12* and *13*), the only significant difference found was between Norplant and DMPA injections. Norplant users had an almost 90% lower rate of discontinuation for this reason (rate ratio, 0.09; 95% CI, 0.49 to 0.33). One RCT,[56] which compared Norplant with Norplant-2, provided single decrement life tables and reported rates at year 1 of 7.1% (SE, ± 2.8) for Norplant users and 10.4% (SE, ± 3.5) for Norplant-2 users. At year 2 the rates were 14.8% (± 3.9%) and 20.4% (± 4.7%), respectively. In this study there was no significant difference between the two intervention groups in menstrual disturbance as a reason to discontinue, with the absolute probability difference being –3.3% (95% CI, –12.09% to 5.49%) at 1 year and –5.6% (95% CI, –17.57% to 6.37%) at 2 years.

With regard to either amenorrhoea or bleeding complaints as reasons for discontinuation, there were no significant differences when Norplant users were compared with IUD users (*Table 14*). A study comparing Norplant with CuT 200 IUDs,[82] found that Norplant users were significantly more likely to discontinue due to overall menstrual disturbance. It was not possible to include these data in the meta-analysis.

TABLE 11 *Hormonal reasons for discontinuation: Norplant compared with other methods*

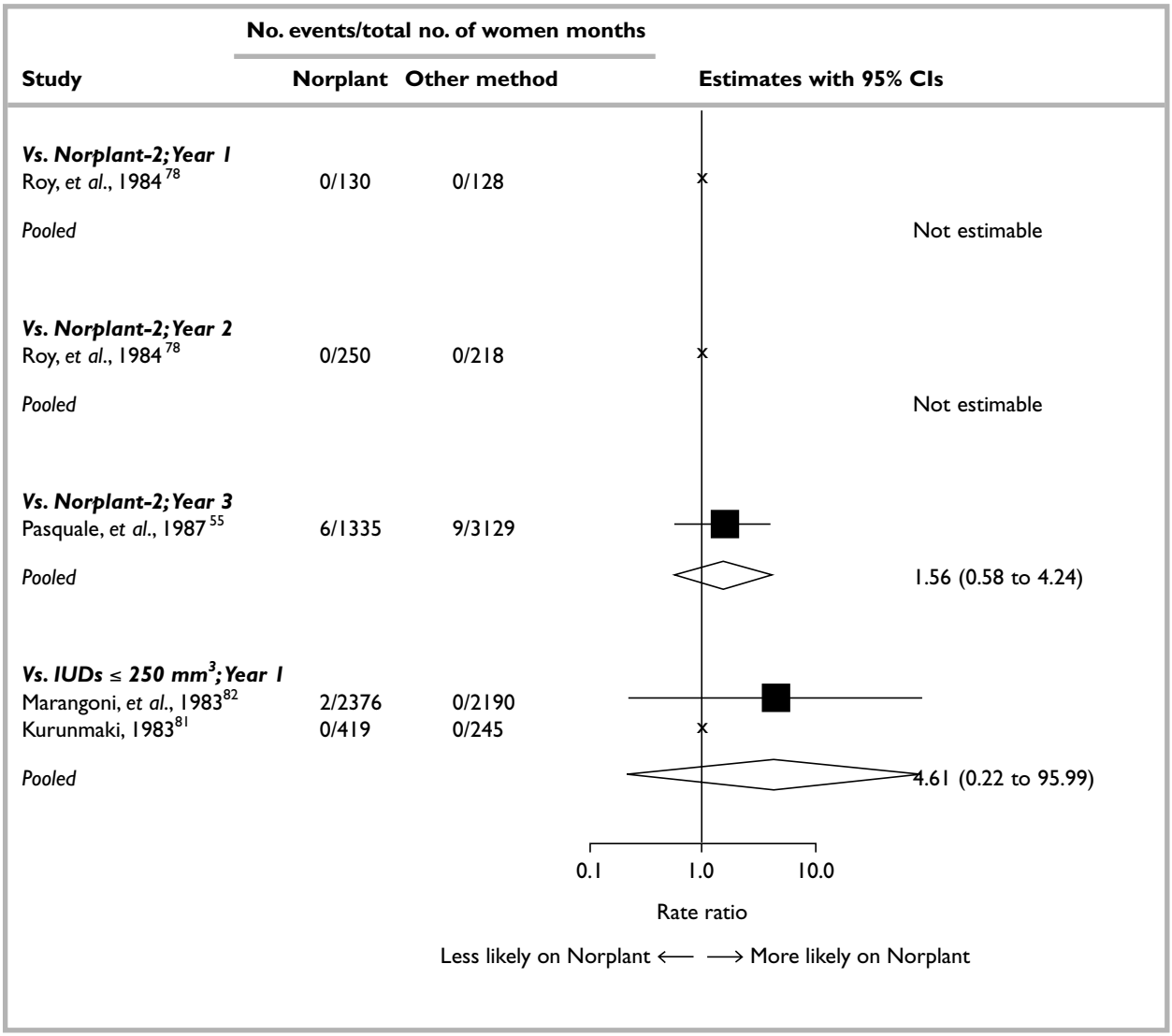
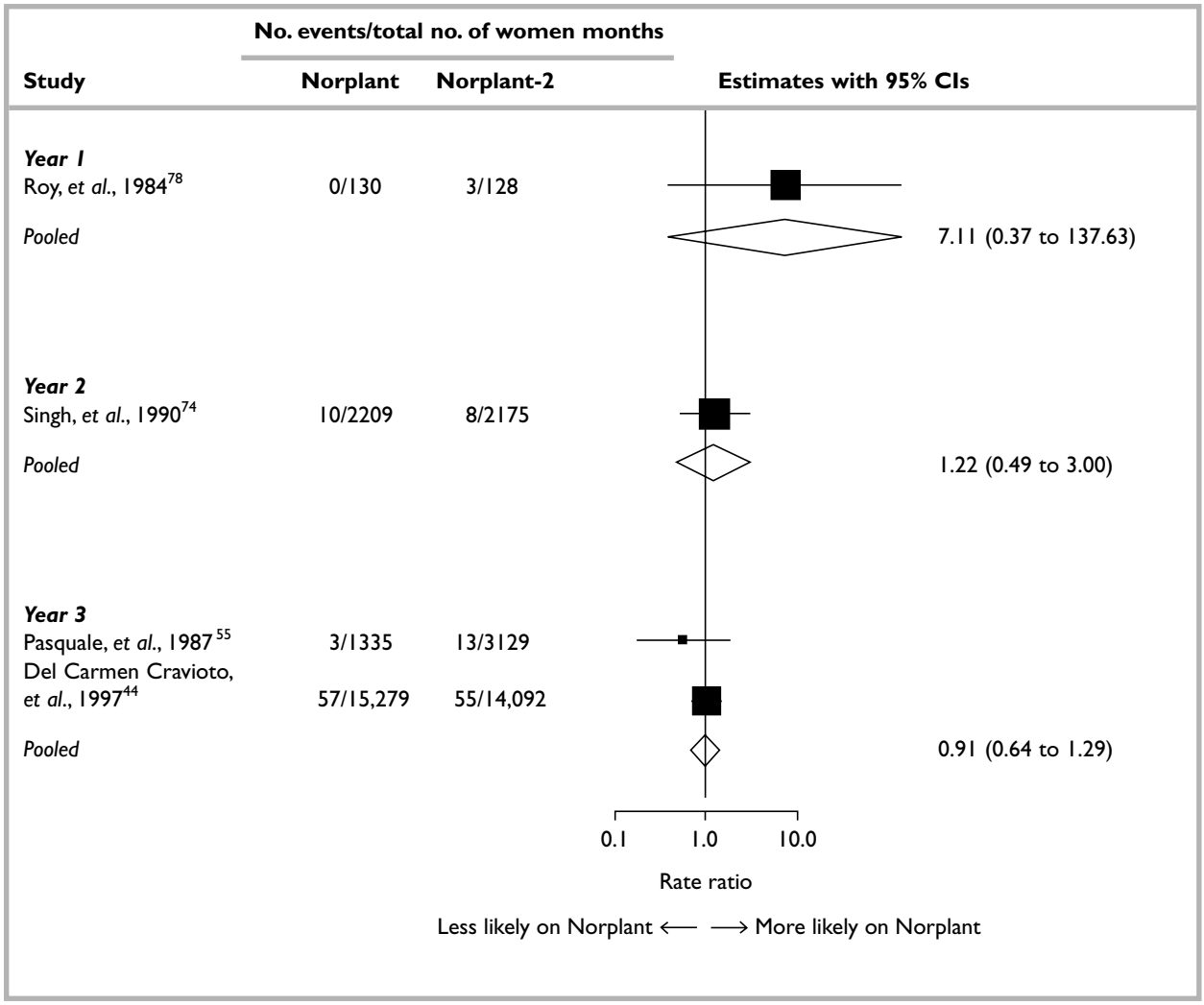


TABLE 12 *Menstrual reasons for discontinuation: Norplant compared with Norplant-2*



Authors of the individual patient meta-analyses of the studies comparing Norplant with Implanon[37] reported that there were marked differences between geographical areas in the rates of discontinuation of method because of menstrual disturbance. Women in Canada and Europe were more likely to discontinue implants because of menstrual disturbance (22.5% discontinuing Norplant and 30.2% discontinuing Implanon for this reason) than were women in South Asia (1.4% discontinuing Norplant and 0.9% discontinuing Implanon). Overall, frequent irregular bleeding was the most common menstrual reason for discontinuing either Norplant (13.7%) or Implanon (15.5%).

Other. Apart from one exception, no significant differences were noted between Norplant and the other contraceptive methods in adverse events, planning pregnancies or 'personal choice' as reasons for discontinuation (*Tables 15–19*). The one exception was that there was nearly a 90% reduction in the rate of discontinuation for personal reasons in Norplant users when compared with pill users.

Norplant-2

As reported above, most of the studies included in the meta-analysis compared Norplant-2 with Norplant. There was one comparison of Norplant-2 with IUSs included in the analysis.[47] In this study, there were no pregnancies after the 3093 women months of follow-up in the Norplant-2 group and one pregnancy, during the first year, after the 3098 women months of follow-up in the LNG-20 IUS group, giving a rate ratio of 0.33 (95% CI, 0.01 to 8.2) at year 3. The continuation rates were similar at year 1, (rate ratio, 1.12; 95% CI, 0.83 to 1.51). There was a suggestion that Norplant-2 users were less likely to experience expulsions (rate ratio, 0.14; 95% CI, 0.01 to 2.7) or ovarian cysts (rate ratio, 0.24; 95% CI, 0.04 to 1.55), although no significant differences were found. There were no diagnoses of breast cancer during the study. There were no significant differences

TABLE 13 *Menstrual reasons for discontinuation: Norplant compared with other methods*

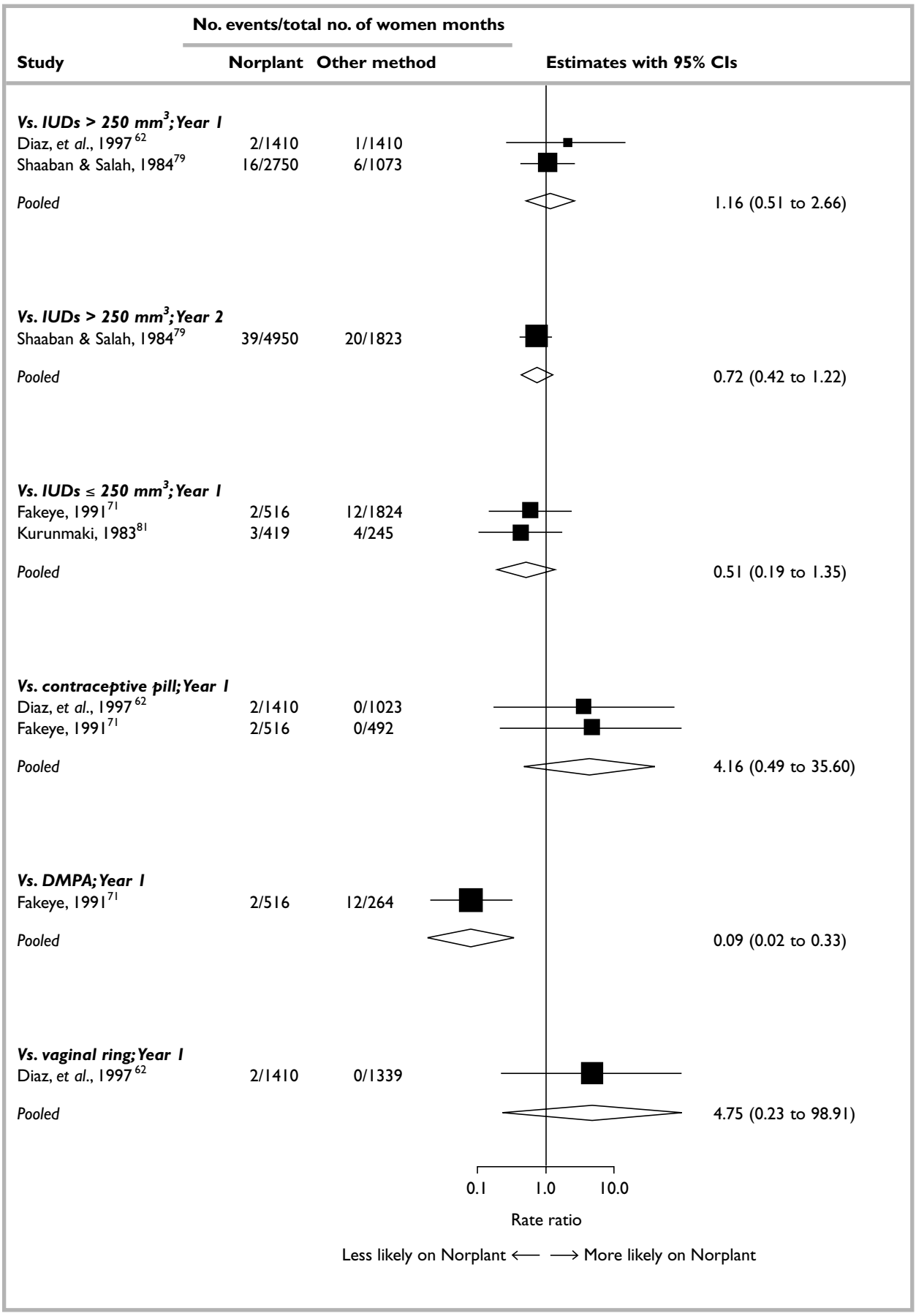


TABLE 14 *Specific menstrual reasons for discontinuation: Norplant compared with other methods*

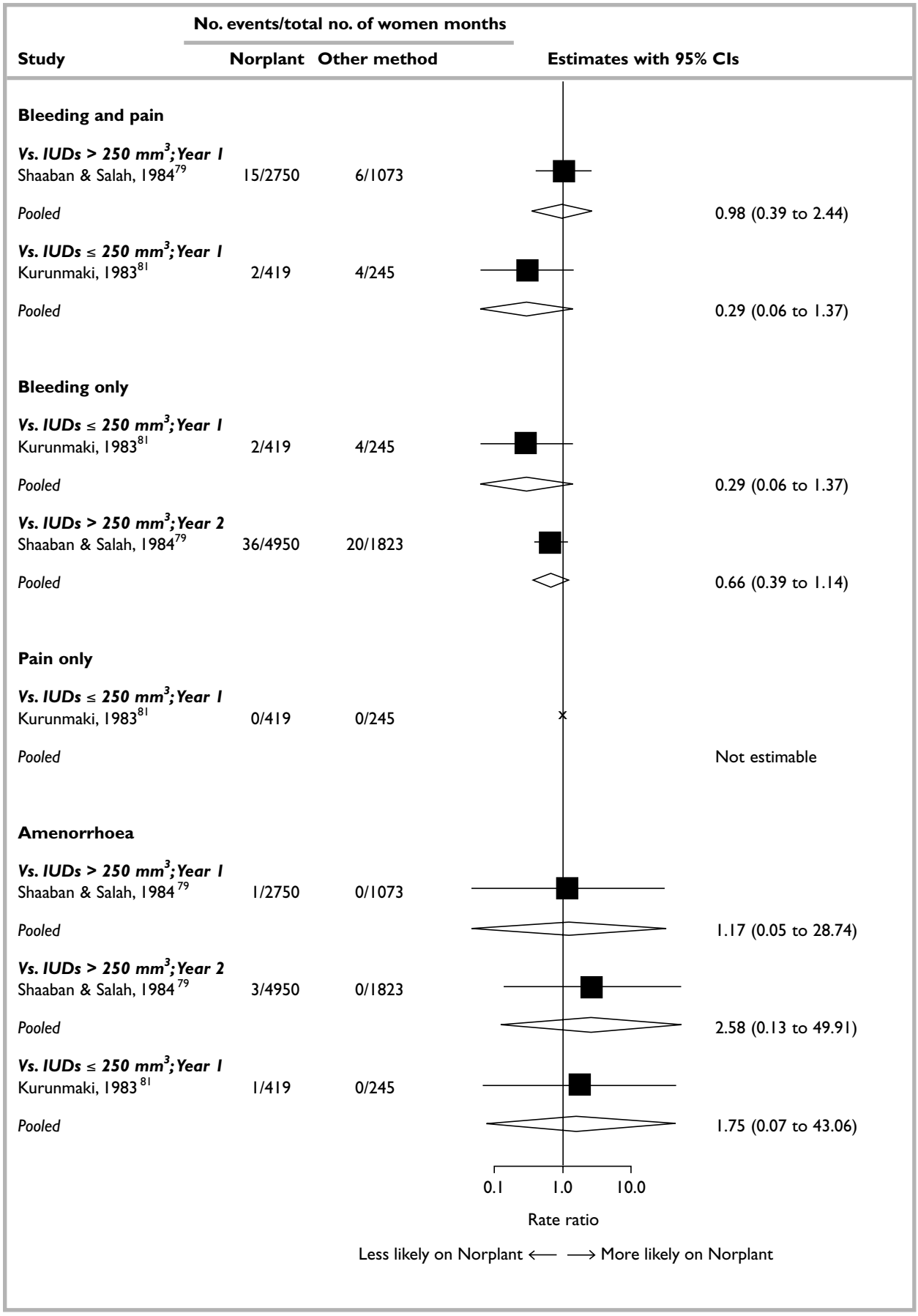


TABLE 15 *Discontinuation due to adverse events: Norplant compared with other methods*

Study	No. events/total no. of women months: Norplant	Other method	Estimates with 95% CIs
Vs. Norplant-2; Year 1			
Roy, *et al.*, 1984[78]	1/130	0/128	
Pooled			2.95 (0.12 to 72.51)
Vs. Norplant-2; Year 2			
Roy, *et al.*, 1984[78]	1/250	0/218	
Pooled			2.62 (0.11 to 64.21)
Vs. Norplant-2; Year 3			
Pasquale, *et al.*, 1987[55]	0/1335	3/3129	
Pooled			0.33 (0.02 to 6.48)
Vs. IUDs ≤ 250 mm^3; Year 1			
Kurunmaki, 1983[81]	0/419	0/245	
Pooled			Not estimable

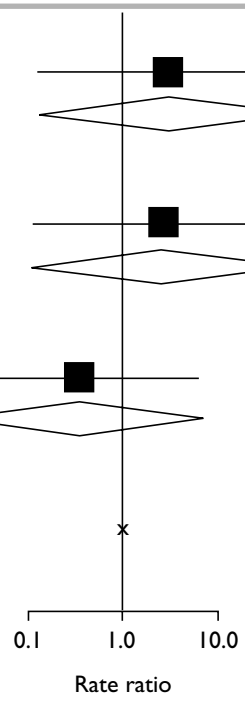


TABLE 16 *Discontinuation due to planned pregnancy: Norplant compared with Norplant-2*

Study	No. events/total no. of women months: Norplant	Norplant-2	Estimates with 95% CIs
Year 1			
Roy, *et al.*, 1984[78]	0/130	0/128	
Pooled			Not estimable
Year 2			
Singh, *et al.*, 1990[74]	10/2209	11/2175	
Roy, *et al.*, 1984[78]	0/250	1/218	
Pooled			0.84 (0.37 to 1.88)
Year 3			
Del Carmen Cravioto, *et al.*, 1997[44]	64/15,279	65/14,092	
Pooled			0.91 (0.64 to 1.28)

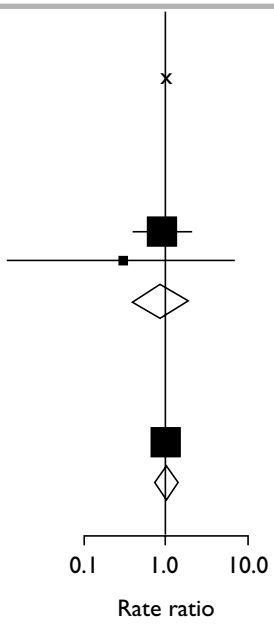
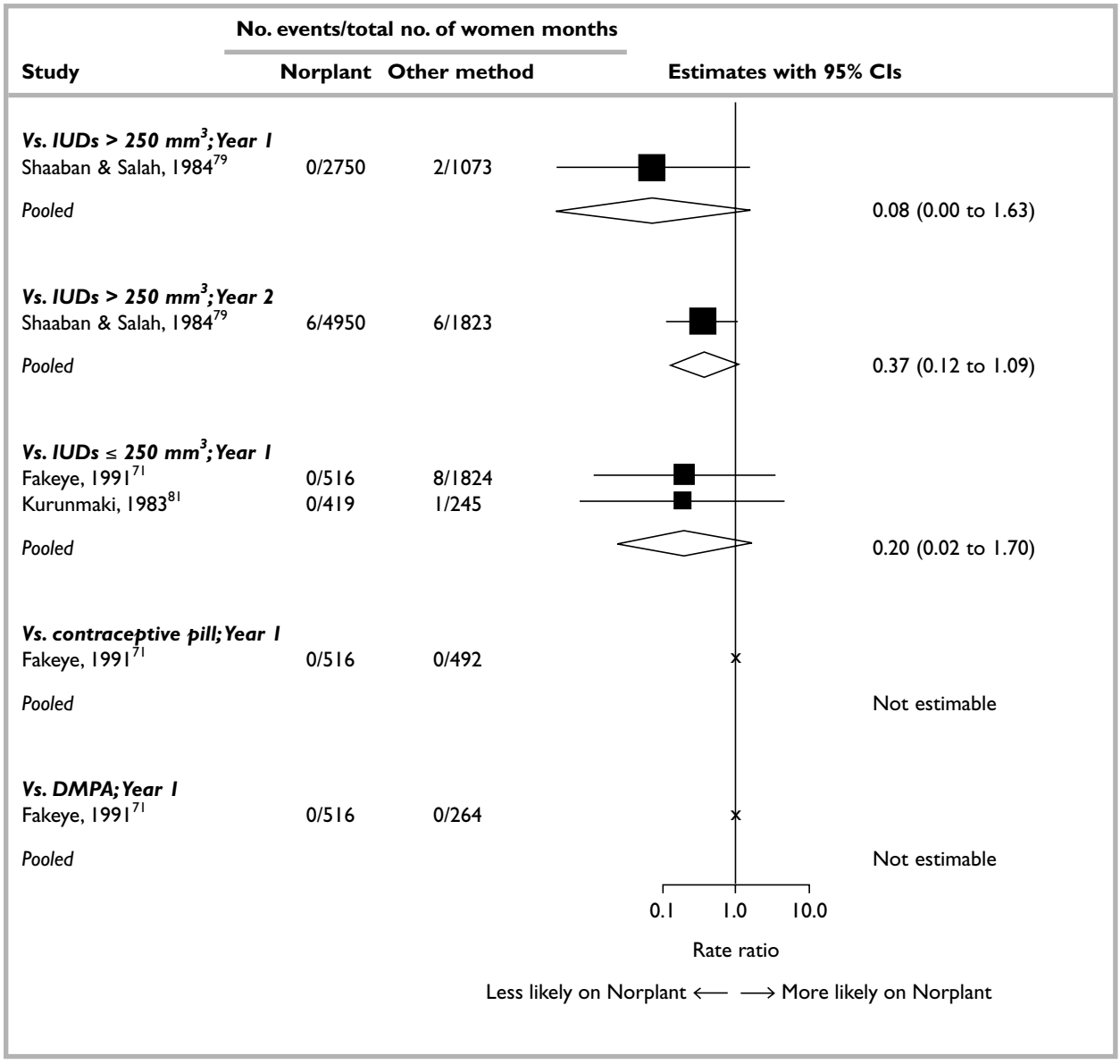


TABLE 17 *Discontinuation due to planned pregnancy: Norplant compared with other methods*



between the intervention groups in reasons given for discontinuing the contraceptive method.

The results from the data extraction for menstrual event are presented in *Table 20*. Norplant-2 users were significantly more likely than LNG-20 IUS users to complain of spotting and prolonged bleeding, but were less likely to complain of amenorrhoea.

Other subdermal implants

There was only one other implant intervention study included in the meta-analysis.[65] This was a comparison of Uniplant* versus the CuT 380A IUD. There were no pregnancies in 1217 women months of Uniplant use and in 1232 women months of CuT 380A IUD use. No significant differences in the rate ratios were observed for any of the other outcomes for which it was possible to extract data: continuation of method (0.97; 95% CI, 0.74 to 1.26), hormonal reasons for discontinuation of method (3.04; 95% CI, 0.12 to 74.55), menstrual reasons for discontinuation (1.01; 95% CI, 0.18 to 5.84) or personal choice (1.01; 95% CI, 0.28 to 3.71).

*Uniplant is a single nomegestrol acetate contraceptive implant. It is not licensed in the UK but it is a contraceptive method offered in some other countries.

TABLE 18 *Discontinuation due to personal choice: Norplant compared with Norplant-2*

Study	No. events/total no. of women months: Norplant	Norplant-2	Estimates with 95% CIs
Year 1			
Roy, *et al.*, 1984[78]	0/130	0/128	
Pooled			Not estimable
Year 2			
Roy, *et al.*, 1984[78]	0/250	0/218	
Pooled			Not estimable
Year 3			
Pasquale, *et al.*, 1987[55]	5/1335	7/1329	
Del Carmen Cravioto, *et al.*, 1997[44]	46/15,279	48/14,902	
Pooled			1.00 (0.69 to 1.46)

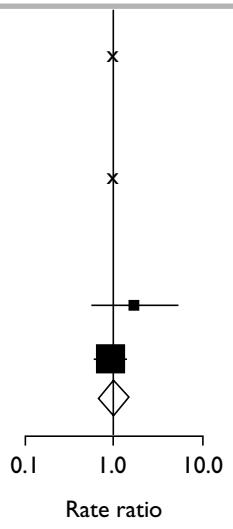


TABLE 19 *Discontinuation due to personal choice: Norplant compared with other methods*

Study	No. events/total no. of women months: Norplant	Other method	Estimates with 95% CIs
Vs. IUDs > 250 mm³; Year 1			
Shaaban & Salah, 1984[79]	4/2750	1/1073	
Pooled			1.56 (0.25 to 9.91)
Vs. IUDs > 250 mm³; Year 2			
Shaaban & Salah, 1984[79]	17/4950	6/1823	
Pooled			1.04 (0.42 to 2.57)
Vs. IUDs ≤ 250 mm³; Year 1			
Fakeye, 1991[71]	1/516	8/1824	
Pooled			0.44 (0.08 to 2.51)
Vs. contraceptive pill			
Fakeye, 1991[71]	1/516	8/492	
Pooled			0.12 (0.02 to 0.68)
Vs. DMPA			
Fakeye, 1991[71]	1/516	0/264	
Pooled			1.53 (0.06 to 37.68)

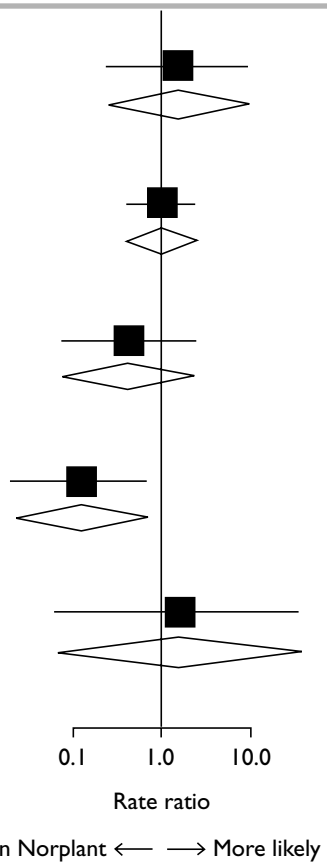


TABLE 20 *Risk ratios for menstrual disturbance in Norplant-2 users relative to LNG-20 IUS users*

Events and follow-up period	No. of events/total no. of women		Risk ratio (95% CI)
	Norplant-2	LNG-20 IUS	
Spotting:			
Year 1	36/96	11/90	3.07 (1.67 to 5.65)
Year 2	22/79	4/79	5.50 (1.99 to 15.23)
Year 3	18/69	3/65	5.65 (1.75 to 18.29)
Oligomenorrhoea:			
Year 1	21/96	30/90	0.66 (0.41 to 1.06)
Year 2	6/79	37/79	0.16 (0.07 to 0.36)
Year 3	8/69	8/65	0.94 (0.36 to 2.36)
Amenorrhoea:			
Year 1	8/96	17/90	0.44 (0.20 to 0.97)
Year 2	0/79	21/79	0.02 (0.001 to 0.38)
Year 3	2/69	5/65	0.38 (0.08 to 1.87)
Prolonged bleeding:			
Year 1	33/96	4/90	7.73 (2.85 to 20.96)
Year 2	24/79	4/79	6.00 (2.18 to 16.50)
Year 3	14/69	2/65	6.59 (1.56 to 27.69)

Chapter 5

Results: hormonally impregnated IUSs

Characteristics of included studies

Twenty-nine intervention studies on hormonally impregnated IUSs met the inclusion criteria outlined in the protocol. Nineteen were RCTs identified from 37 publications and 11 were non-randomised prospective cohort comparisons, with no duplicate publications. One study was made up of two clinic populations, with one clinic randomising women to intervention and the other not.[85] *Tables 21* and *22* show the characteristics of all studies that met the inclusion criteria.

Overall, 46% of studies were conducted in developing countries, 35% were carried out in developed countries, and the remaining 19% of studies were international multicentre studies that were conducted in both developed and developing countries. The majority of women in the studies included in this review lived in developing countries – twice as many living in developing countries than developed countries in the RCTs (8342 versus 3874 women recruited, respectively), and nearly ten times more living in developing countries than developed countries in the non-RCT cohort studies (2967 women versus 312 women recruited, respectively). The majority of women (11,636 in total) in the RCTs were recruited for international studies conducted across both developing and developed countries. From the publications for three of the studies[113,120,124] it was not possible to determine the countries in which the studies were carried out. Five studies were conducted in hospital settings.[85,100,110,118,119]

The age range of participants was 14–49 years. None of the studies confined entry to specific age requirements, other than ensuring that the women recruited were of reproductive age.

Nineteen studies limited recruitment to women with proven fertility.[43,47,73,85,98–101,105,106,108,110,114,117–120,122,125] Five studies recruited women immediately after giving birth or after abortion.[100,106,110,118,119] One of these studies restricted recruitment to women who were breastfeeding.[110] Six studies (20%) stated that they only included women with a regular menstrual cycle.[87,98,115,120–122]

Nearly all of the studies, for both the RCTs and the non-randomised prospective cohorts, were either comparisons of IUSs with different hormonal dosage release rates or of IUSs versus non-hormonal IUDs. The two exceptions were studies by Wang and colleagues[47] who compared the LNG-20 IUS with Norplant-2, and Sivin and colleagues[72] who investigated return to fertility after discontinuation of subdermal implants, IUSs or IUDs.

In three of the ten cohort studies,[117,121,122] the enrolled groups were reported to be similar at entry. Four studies did not state whether or not the populations were similar.[119,121–123] It was difficult to ascertain, from the studies in which differences in the populations were described, if women who chose hormonal IUSs were in fact different from women who chose alternative contraceptive methods (see *Table 22*).

It was documented in three of the 29 studies that contraceptive counselling was provided.[43,47,123] None of the studies mentioned any specific training for the healthcare workers who inserted the devices. Fourteen studies provided information on the date of device insertion and all devices were inserted within appropriate time frames.[43,47,73,98,101,106,110,111,114,118–120,123,125]

Excluded studies

Seventeen studies identified from 18 publications were excluded from the review (see appendix 5). A further three papers[126–128] were excluded because they reported outcomes that were not relevant to the review, but other publications of the same studies did meet the inclusion criteria. The most common reason for excluding a paper was that the outcomes reported were not relevant to the review (71%).

Quality

Once the nine non-English or non-French publications,[49,91,111,117,119,121–123,125] the summary report[86] and the abstract[112] were removed, having been assessed by RF and translators, complete initial agreement between the two reviewers on all quality

TABLE 21 *Characteristics of included studies on IUSs: RCTs*

Study*†	Setting	Description of participants	No. randomised	Intervention (no. randomised)	Primary outcomes	Length of follow-up
WHO, 1997[86]	International multicentre (20 centres)	Not stated	3384	LNG-IUS (20 µg/day) (*n* = 1693) CuT 380A IUD (*n* = 1691)	Pregnancy Continuation Reasons for discontinuation	Ongoing (4 centres have reached 5-year follow-up)
Pakarinen, *et al.*, 1996[87]	Finland FPCs	Age: 18–43 years Variable parity Regular menses	298	LNG-IUS (20 µg/day) (*n* = 147) LNG-ICD (20 µg/day) (*n* = 151)	Pregnancy Continuation Reasons for discontinuation Hormonal side-effects	1 year
***Andersson, *et al.*, 1994[43]** Rybo, *et al.*, 1993[88] Andersson, *et al.*, 1992[89] Toivonen, *et al.*, 1991[90] Lahteenmaki, *et al.*, 1991[91] (Finland only) Luukkainen, *et al.*, 1987[92]	Multinational (Denmark, Finland, Hungary, Norway and Sweden) 12 FPCs	Age: 18–38 years Parous Not breastfeeding	2758	LNG-IUS (20 µg/day) (*n* = 1821) Nova-T IUD (*n* = 937)	Pregnancy Continuation Reasons for discontinuation Adverse events Hormonal side-effects Pregnancy after discontinuation of method[89]	5 years
***Sivin & Stern, 1994[73]** Sivin, *et al.*, 1991[93] Sivin, *et al.*, 1990[94] Sivin, *et al.*, 1987[95] Belhadj, *et al.*, 1986[96] (subset of RCT) Sivin, *et al.*, 1984[97]	Multinational (Singapore, Brazil, Egypt and USA) FPCs	Age: 18–38 years Parous	2226	LNG-IUS (20 µg/day) (*n* = 1125) CuT 380Ag IUD (*n* = 1121)	Pregnancy Continuation Reasons for discontinuation Insertion problems Hormonal side-effects Menstrual disturbance Adverse events Pregnancy after discontinuation of method[96]	7 years
***Wang, *et al.*, 1992[47]** Gao, *et al.*, 1990[48] Wang, *et al.*, 1990[49]	China FPC	Age: 20–40 years Parous Not breastfeeding	200	LNG-IUS (20 µg/day) (*n* = 100) Norplant rods (30 µg/day) (*n* = 100)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	3 years
***Baveja, *et al.*, 1989[98]**	India FPCs	Age: 18–40 years Proven fertility Regular menses	2118	LNG-IUS (20 µg/day) (*n* = 475) CuT 380Ag IUD (*n* = 434) CuT 220C IUD (*n* = 496) CuT 200B IUD (*n* = 500)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	3 years
Andrade, *et al.*, 1988[85] (Chile group only. Brazil group not randomised – see non-RCTs)	Chile (Brazil group excluded) Hospital	Parous	150	Progestasert (*n* = 49) Lippes loop IUD (*n* = 51) Cu 7 IUD (*n* = 50)	Menstrual blood loss Iron status	2 years

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

continued

TABLE 21 contd *Characteristics of included studies on IUSs: RCTs*

Study*†	Setting	Description of participants	No. randomised	Intervention (no. randomised)	Primary outcomes	Length of follow-up
WHO, 1987[99]	Multinational (Thailand, China, India, Vietnam, Cuba, Russia, Yugoslavia and Zambia) Various departments	Age: 16–40 years Parous	4182	LNG-IUS (2 µg/day) (*n* = 1377) CuT 220C IUD (*n* = 1412) Nova-T IUD (*n* = 1393)	Pregnancy Continuation Reasons for discontinuation	2 years
Lavin, *et al*., 1983[100]	Chile Maternity unit	*Post partum*	400	Progestasert (*n* = 200) CuT 200 IUD (*n* = 200)	Pregnancy Continuation Menstrual disturbance	1 year
*__Nilsson, *et al*., 1983__[101] Luukkainen, *et al*., 1986[102] (Finland only) Nilsson, *et al*., 1982[103] Nilsson, *et al*., 1981[104]	Finland and Brazil FPCs	Age: 18–40 years Proven fertility Not breastfeeding	484	LNG-IUS (20 µg/day) (*n* = 164) LNG-IUS (30 µg/day) (*n* = 163) Nova-T IUD (*n* = 157)	Pregnancy Continuation Reasons for discontinuation Hormonal side-effects Menstrual disturbance	2 years (Finland and Brazil) 5 years (Finland only)
Rybo, *et al*., 1983[105]	France	Age: 24–42 years Multiparous	30	Progestasert (*n* = 13) CuT 200 IUD (*n* = 17)	Pregnancy Menstrual disturbance and blood loss	< 1 year
WHO, 1983[106] Chompootaweep, *et al*., 1986[107] (subset – Thailand only)	Multinational (13 countries) FPCs	Age: 16–40 years Two groups: 1. Parous, 'interval insertion' 2. Insertion after abortion	2514 3028	Alza T IPCS 52 (*n* = 1254) CuT 220C IUD (*n* = 1260) Alza T IPCS 52 (*n* = 985) CuT 220C IUD (*n* = 1032) Multiload IUD (*n* = 1011)	Pregnancy Continuation Reasons for discontinuation	2 years
el Mahgoub, 1982[108] el Mahgoub, 1980[109]	Egypt FPCs	Age: 15–40 years Parous Hormonal contraceptive users and immediate *post partum* excluded	300	LNG-IUS (10 µg/day) (*n* = 100) Norgestrel T IUS (various doses) (*n* = 100) CuT 200 IUD (*n* = 100)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance and blood loss Endometrial and cervical cell changes	3 years
Heikkila, 1982[110]	Finland Hospital (maternity unit)	*Post partum* Amenorrhoeic Breastfeeding	80	LNG IUS (30 µg/day) (*n* = 40) Nova-T IUD (*n* = 40)	Pregnancy Continuation Reasons for discontinuation Hormonal side-effects Menstrual disturbance LNG plasma concentration	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

continued

TABLE 21 contd *Characteristics of included studies on IUSs: RCTs*

Study*†	Setting	Description of participants	No. randomised	Intervention (no. randomised)	Primary outcomes	Length of follow-up
*Larsen, *et al.*, 1980[111]	Denmark	Age: 15–44 years Various parity	382	Progestasert (65 µg/day) (*n* = 196) CuT 200 IUD (*n* = 186)	Pregnancy Continuation Reasons for discontinuation	1 year
Affandi, *et al.*, 1980[112]	Indonesia	Not known	697	Progestasert (*n* = 72) Cu T 200 IUD (*n* = 75) Cu7 IUD (*n* = 75) Lippes loop IUD (*n* = 75)	Pregnancy Reasons for discontinuation	2 years
*Newton, *et al.*, 1979[113]	4 clinics	Various parity	676	Progestasert (65 µg/day) (*n* = 359) Inert IUD (*n* = 317)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	1 year
Pizarro, *et al.*, 1979[114] Pizarro, *et al.*, 1977[115]	Chile FPC	Age: 17–40 years Parous Regular menses	295	Progesterone T IUS (65 µg/day) (*n* = 146) Cu 7 IUD (*n* = 149)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	1 year
*Fylling & Fagerhol, 1979[116]	Denmark	Mixed parity	326	Progestasert (*n* = 162) Nova-T IUD (*n* = 164)	Pregnancy Continuation Reasons for discontinuation Serum immuno-globulin levels	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

assessment factors was 50% (19/38). There was greater agreement for RCTs (53%; 18/34) than for non-RCT studies (25%; 1/4). As with the quality assessment for the subdermal implant studies, the disagreement was more often on factors related to contraceptive-specific issues than on factors related to general study design. All of the reviewer differences were resolved after discussion.

RCTs

Two trials were identified, one from a conference abstract[112] and the other a progress summary,[86] for which no subsequent publications were found. Therefore it was not appropriate to include them in the quality assessment.

Of the remaining 17 trials, ten provided information on method of randomisation (see appendix 6).[43,47,73,85,87,98,99,101,106,114] Eight trials documented that allocation of contraceptive method was concealed to the investigator,[43,47,73,87,98,99,106,113] but in only three studies was assessment of outcomes blinded.[101,113,114] Women remained blind to allocated method in an additional two studies.[43,111] In 14 studies, the compared groups were treated identically in terms of measurement of outcomes.[43,47,73,87,98–100,101,105,106,111,113,114,116] A description of the characteristics of women lost to follow-up or who withdrew from the study was not provided in any of the publications.

Twelve studies used life-table analysis to determine pregnancy and continuation rates.[43,47,73,87,98,99,101,106,108,111,113,114] It was possible to determine whether single or multiple decrement probabilities had been reported in nine of these studies and eight gave single decrement probabilities.

Less than half of all included studies provided information about contraceptive methods used (or pregnancy) immediately before enrolment. In the 15 studies in which pregnancy occurred,[43,47,73,87,98–101,105,106,108,111,113,114,116] nine distinguished between user or method failure (or both).[43,47,73,87,98,99,101,106,114] Active follow-up was conducted in three of the 17 studies.[73,99,106]

TABLE 22 *Characteristics of included studies on IUSs: non-randomised prospective cohorts*

Study*†	Setting	Description of participants	No. enrolled	Intervention (no. per group)	Primary outcomes	Group comparability at entry	Length of follow-up
Diaz, *et al.*, 1992[117]	Brazil FPC	Parous	402	LNG-IUS (20 µg/day) (*n* = 202) CuT 380A IUD (*n* = 200)	Pregnancy Continuation Reasons for discontinuation	Similar at entry	5 years
Sivin, *et al.*, 1992[72]	International FPCs	Mean age: 27.8 years Cohort from RCTs discontinuing contraception to become pregnant Variable parity	372	LNG-IUS (20 µg/day) (*n* = 91) CuT 380Ag (*n* = 103) (See Sivin & Stern, 1994[73]) Norplant (*n* = 62) Norplant-2 (*n* = 116) (See Olsson, *et al.*, 1988[58])	Pregnancy after discontinuation of method	Norplant users older than Norplant-2 users and had been using method for a shorter period of time than CuT 380Ag IUD users	2 years
Andrade, *et al.*, 1988[85] (see RCTs)	Chile and Brazil Hospital	Variable parity	395	Progestasert (*n* = 49) Lippes loop IUD (*n* = 117) Multiload-250 IUD (*n* = 26) Multiload-375 IUD (*n* = 74) CuT 200 IUD (*n* = 61) T-Chloroquin IUD (*n* = 18) Cu 7 IUD (*n* = 50)	Menstrual blood loss Iron status	Cu 7 IUD users only recruited from Chile centre and CuT 200 and T-Choroquin IUD users only recruited from Brazil centre	2 years
*__Heikkila, *et al.*, 1982__[118]	Finland Hospital (maternity unit)	After abortion (6–11 weeks gestation)	60	LNG-IUS (10 µg/day) (*n* = 30) Nova-T IUD (*n* = 30)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance Hormonal profile	LNG-IUS women older, lower gestation at time of abortion, higher parity, more likely to be married and more likely to have used IUD previously. In addition, LNG users were selected if they had had past difficulty with other contraceptive methods	1 year
*__Reynoso, *et al.*, 1982__[119]	Mexico Dept of Obstetrics and Gynaecology (hospital)	Age: 14–49 years *Post partum*	1020	Progestasert (*n* = 196) CuT 220 IUD (*n* = 101) CuT 200 IUD (*n* = 180) Lippes loop IUD (*n* = 407) Multiload 250 IUD (*n* = 136) (Different insertion techniques compared)	Pregnancy Continuation Reasons for discontinuation	Not stated	1 year
Diaz, *et al.*, 1980[120]	Not stated	Age: 18–38 years Parous Regular menses	765	Hormone-impregnated IUSs: MA‡ (*n* = 245) LNG‡ (*n* = 105) Norethindrone (*n* = 155) R2323‡ (*n* = 58) Norgestrienone (*n* = 31) IUDs: BaSO4 (*n* = 71) CuT 200 (*n* = 100)	Pregnancy Continuation Reasons for discontinuation Recovery of fertility after discontinuation	$BaSO_4$ IUD users aware of device's lesser contraceptive effectiveness	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*
‡ *Various daily release doses*

continued

TABLE 22 contd *Characteristics of included studies on IUSs: non-randomised prospective cohorts*

Study*†	Setting	Description of participants	No. enrolled	Intervention (no. per group)	Primary outcomes	Group comparability at entry	Length of follow-up
Feichtinger, *et al.*, 1980[121]	Austria FPC	Variable parity	146	Progestasert IUS (65 µg/day) (*n* = 73) CuT 200 IUD (*n* = 73)	Pregnancy Continuation Reasons for discontinuation	Similar at entry	1 year
Pizarro Orchard, *et al.*, 1980[122]	Chile FPCs	Age: 17–40 years Multiparous Regular menses	295	Progestasert IUS (65 µg/day) (*n* = 146) Cu 7 IUD (*n* = 149)	Pregnancy Continuation Menstrual disturbance	Similar at entry	1 year
Gozzi & Quadrani, 1977[123]	Italy	Age: 19–42 years Mixed parity Not wanting children for next 5 years	106	IUDs: Cu 7 with MA (30 mg) (*n* = 37) Cu 7 (*n* = 56) CuT 200 (*n* = 13)	Pregnancy Continuation Reasons for discontinuation	Not stated	1–2 years
Nilsson, 1977[124]	Not stated	Age: 25–39 years Regular menses	18	d-Ng IUS, surface area 83 mm^2 (*n* = 11) d-Ng IUS, surface area 132 mm^2 (*n* = 7)	Menstrual disturbance Ovarian function Plasma concentrations of d-Ng	Not stated	< 3 months
Martinez Manautou, *et al.*, 1976[125]	Mexico FPCs	Multiparous	855	Progestasert IUS (65 µg/day) (*n* = 697) Progestasert IUS (40 µg/day) (*n* = 158)	Pregnancy Continuation Reasons for discontinuation Menstrual disturbance	Not stated	1 year

* *Studies marked with an asterisk were included in the meta-analysis*
† *Studies in bold are the most recent publications and the ones that are referred to in the rest of the text*

Non-randomised prospective cohort studies

In five of the ten non-RCTs[72,120–122,125] included in the review, it was clear that the comparative groups had been treated in the same way in terms of investigations and follow-up visits. None of the studies reported that the investigators were blinded to contraceptive method when assessing outcomes.

Follow-up rates were similar in seven studies,[72,117,119,120,122,124,125] but none of the studies provided a demographic description of women who withdrew from the study or were lost to follow-up.

One study[118] restricted enrolment to women after abortion but in other studies there was no attempt to control for confounding in study design. There was no stratification of results or regression analysis to explore the effect of confounders in any of the studies.

Life-table analysis was used in six of the nine studies in which pregnancy and/or continuation rates were reported.[72,117,119,120,122,125] It was not possible to determine whether single or multiple decrement probabilities had been used to report outcomes in any of these studies.

A description of contraceptive method used before enrolment was given in seven studies.[72,117–119,121–123] Only one of the studies[118] provided sufficient information about the potential cause of contraceptive failure. None of the investigators conducted active follow-up analysis.

Quality differences between the randomised and non-randomised studies

The only significant difference in quality between the RCTs and non-RCTs, other than study design, was that RCTs were more likely to use (or clearly document) single decrement life tables to report pregnancies and continuation.

Quantitative synthesis

Data from nine studies (marked with asterisks in *Tables 21* and *22*) were synthesised, 42% of the RCTs[43,47,73,98,101,111,113,116] and 9% of the non-randomised prospective comparative studies.[119] Eight of the studies where data were not pooled were interventions of prototypes,[99,106,108,110,118,120,123,124] and in the remaining studies it was not possible to extract data in the manner described in the methods.[62,85–87,100,105,112,114,115,121,122,125]

Data from different interventions were pooled only when the methods of comparison were similar. Therefore data from studies comparing the LNG-20 IUS with IUDs > 250 mm^3 were pooled and data from studies comparing the LNG-20 IUS with the IUDs ≤ 250 mm^3 were pooled. These categorisations for IUDs were based on the surface area of the copper wire.

It was thought appropriate to include the data from the study by Heikkila,[110] in which at enrolment the women were amenorrhoeic and breastfeeding, because these factors should not impact on the relative effectiveness of the two investigated interventions as the women were randomised to contraceptive methods.

Meta-analysis

LNG-IUS 20 (Mirena)

Five of the seven studies comparing the LNG-20 IUS with other contraceptive methods were included in the meta-analysis.[43,47,73,98,101] There were two comparisons of the LNG-20 IUS with IUDs > 250 mm^3,[73,98] one with Norplant-2[47] and three with IUDs ≤ 250 mm^3.[43,98,101] All of these studies were RCTs. The outcomes of the comparison of the LNG-20 IUS with Norplant-2 have been reported in chapter 4 (page 28). It was not possible to synthesise data in the remaining two studies which met the inclusion criteria because neither the number of women months at follow-up nor the SEs of the life-table probabilities were reported.[86,87]

Pregnancy

Table 23 shows the summary single decrement life-table differences for pregnancy and *Tables 24–26* provide the summary rate ratios for pregnancy. It appeared that after 5 years of documented follow-up, the LNG-20 IUS was no more or less effective in preventing pregnancy than were the IUDs > 250 mm^3. There was some indication that the LNG-20 IUS is more effective at years 2 and 3, but the difference was not statistically significant.

There was a significant effect when the LNG-20 IUS was compared with IUDs ≤ 250 mm^3 at all of the follow-up years, with a reduction of over 90% in the pregnancy rate by 5 years. Heterogeneity was evident between studies comparing the LNG-20 IUS with IUDs ≤ 250 mm^3 when 1-year data were synthesised. When focusing on the single decrement life-table differences, the significant difference between the LNG-20 IUS and IUDs ≤ 250 mm^3 was no longer evident, with there being an absolute reduction of only 0.5% after 3 years in LNG-20 IUS users compared with IUD ≤ 250 mm^3 users (95% CI, –1.3% to 0.18%). The single decrement life-table probabilities were extracted from one study[98] (see *Table 23*). The pregnancy rate ratio for this study alone was not significant, at year 3 being 0.08 (95% CI, 0.00 to 1.34).

Due to the extremely wide CIs for the rate ratios for LNG-20 IUS users compared with users of the higher dose LNG-IUS (30 µg/day), it was impossible to reach any conclusions about the relative contraceptive effectiveness of these two IUSs.

Continuation of method

The continuation rates for the included studies with the various comparisons are illustrated in *Tables 27* and *28*. There was evidence of heterogeneity of the results in the LNG-20 IUS versus IUD ≤ 250 mm^3 studies at year 1.

The summary rate ratios suggested that continuation with the LNG-20 IUS was similar to continuation with any of the other methods. However at year 5, LNG-20 users were 16% more likely than IUD ≤ 250 mm^3 users to continue, and statistical significance was just reached. The single decrement life-table data from one study[73] suggested that LNG-20 IUS users were significantly less likely to continue with the method compared with CuT 380Ag IUD users. The life-table probabilities for the LNG-20 IUS compared with the CuT 380Ag IUD at 1, 2 and 5 years were 73.5% (SE, ± 1.4) versus 79.8% (± 1.3), 59.4% (± 1.6) versus 67.5% (± 1.5) and 33.0% (± 1.5) versus 40.6% (± 1.6), respectively. Therefore, the differences in continuation probabilities were –6.3% (95% CI, –10.0% to –2.56%) after 1 year, –8.1% (95% CI, –12.4% to –3.8%) after 2 years and –7.6% (95% CI, –11.9% to –3.3%) after 5 years.

Rate of pregnancy after removal

No significant differences were observed in the calculated relative risks for planned pregnancy after removal of the LNG-20 IUS compared with

TABLE 23 *LNG-20 IUS compared with other IUDs: synthesis of single decrement life-table probabilities for pregnancy*

Follow-up period and studies	Single decrement life-table probability (± SE)		Measurement of true effect (± SE)
	LNG-20 IUS vs.	**IUD > 250 mm^3**	
Year 1			
Sivin & Stern, 1994[73]	0.3 (± 0.2)	0.3 (± 0.2)	0.0 (± 0.08)
Baveja, *et al.*, 1989[98]	0.0 (± 0.4)	0.8 (± 0.4)	–0.8 (± 0.32)
			Summary, –0.16 (95% CI, –0.65 to 0.34)
Year 2			
Baveja, *et al.*, 1989[98]	0.0 (± 0.5)	1.0 (± 0.5)	–1.0 (± 0.5)
			Summary, –1.0 (95% CI, –2.39 to 0.39)
Year 3			
Baveja, *et al.*, 1989[98]	0.0 (± 0.5)	1.0 (± 0.5)	–1.0 (± 0.5)
			Summary, –1.0 (95% CI, –2.39 to 0.39)
Year 5			
Sivin & Stern, 1994[73]	1.1 (± 0.5)	1.4 (± 0.4)	–0.3 (± 0.41)
			Summary, –0.3 (95% CI, –1.56 to 0.96)
	LNG-20 IUS vs.	**IUD ≤ 250 mm^3**	
Year 1			
Baveja, *et al.*, 1989[98]*	0.0	0.0	–
Baveja, *et al.*, 1989[98]†	0.0 (± 0.4)	0.9 (± 0.4)	–0.9 (± 0.32)
			Summary, –0.9 (95% CI, –0.2 to 0.2)
Year 2			
Baveja, *et al.*, 1989[98]*	0.0	0.0	–
Baveja, *et al.*, 1989[98]†	0.0 (± 0.4)	0.9 (± 0.4)	–0.9 (± 0.32)
			Summary, –0.9 (95% CI, –0.2 to 0.2)
Year 3			
Baveja, *et al.*, 1989[98]*	0.0 (± 0.3)	0.3 (± 0.3)	–0.3 (± 0.18)
Baveja, *et al.*, 1989[98]†	0.0 (± 0.6)	1.6 (± 0.6)	–1.6 (± 0.72)
			Summary, 0.56 (95% CI, –1.3 to 0.18)

* *Compared with CuT 220C IUD*
† *Compared with CuT 200B IUD*

non-hormonal IUDs. The relative risk for planned pregnancy after 1 year for ex-LNG-20 IUS users compared with ex-IUD > 250 mm^3 users was 1.05 (95% CI, 0.83 to 1.33).[73] The relative risks for ex-LNG-20 IUS users when compared with ex-IUD ≤ 250 mm^3 users were 1.07 (95% CI, 0.88 to 1.32) and 1.07 (95% CI, 0.9 to 1.28) after 1 and 2 years, respectively.[43]

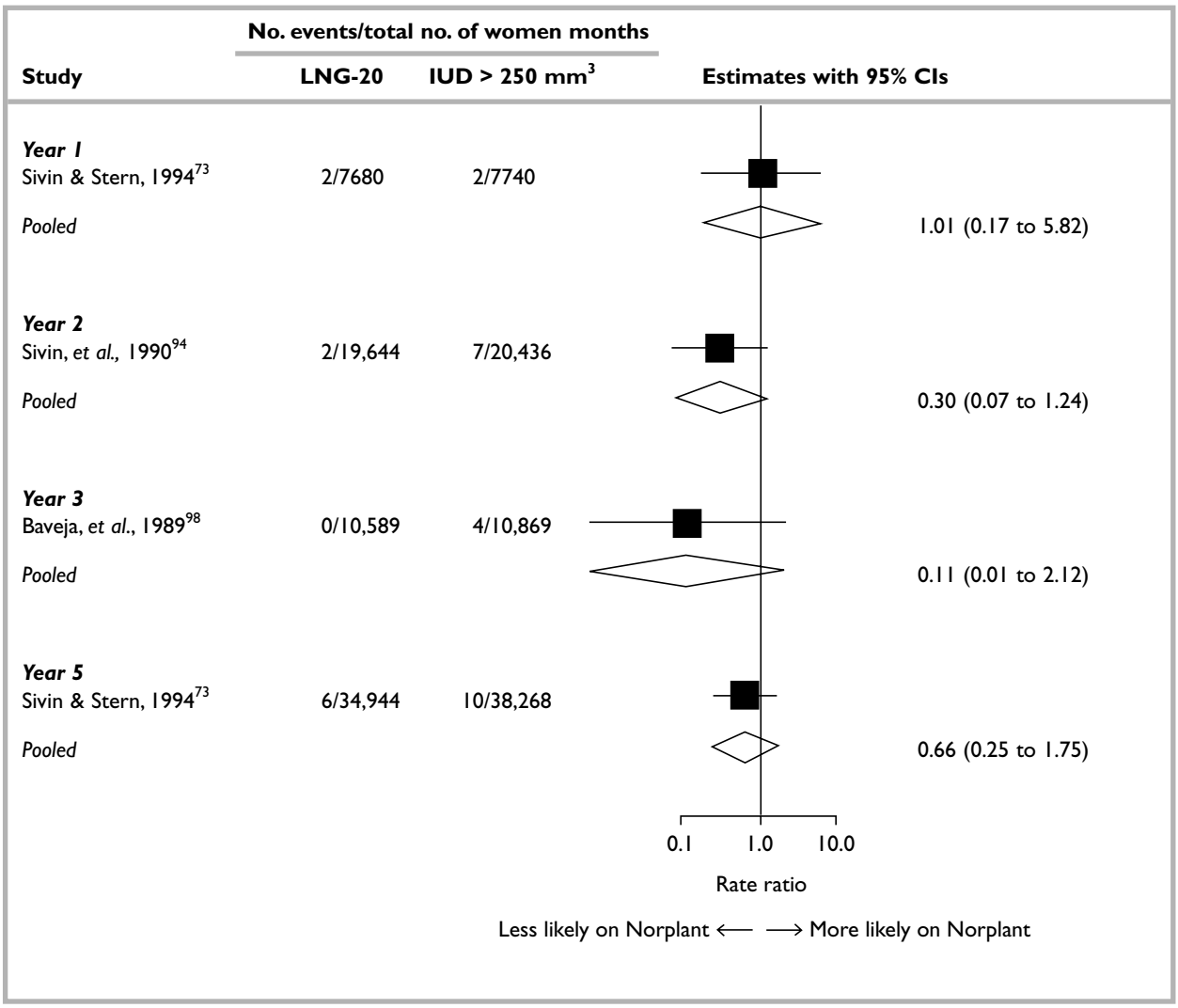
Hormonal side-effects

It was only possible to extract data on hormonal side-effects from one study, by Andersson and colleagues,[43] which compared the LNG-20 IUS with the Nova-T IUD. At 5 year follow-up the relative risk was 1.5 (95% CI, 0.51 to 4.4) for ovarian cysts, 1.71 (95% CI, 0.49 to 6.02) for headaches, 1.5 (95% CI, 0.31 to 7.17) for breast tenderness, 5.56 (95% CI, 0.73 to 42.35) for acne, and 5.0 (95% CI, 95% CI, 0.24 to 103.86) for nausea. Nilsson and colleagues[101] observed that women using the LNG-20 IUS were significantly more likely to report an increase in headaches and acne than women using the Nova-T IUD, but it was not possible to extract these data for the meta-analysis.

Menstrual disturbance

It was possible to extract data on menstrual disturbance outcomes from one study.[73] Data from this study indicated that women using LNG-20 IUSs were more likely to experience amenorrhoea than women using CuT 380Ag IUDs

TABLE 24 *Pregnancy: LNG-20 IUS (Mirena) compared with IUDs > 250 mm³*



and that this risk increased over time. At 3 months the relative risk was 2.15 (95% CI, 1.31 to 3.56) which increased to 7.24 (95% CI, 4.14 to 12.65) at the 3 year follow-up. No significant differences were noticed between LNG-20 IUSs and CuT 380Ag IUDs in terms of prolonged bleeding, the relative risks for which were 0.9 (95% CI, 0.62 to 1.30) at 3 months and 0.1 (95% CI, 0.01 to 2.06) at 3 years.

It was not possible to extract data for meta-analysis on any of the other menstrual disturbance outcomes, but the study by Sivin and colleagues[73] also reported that LNG-20 IUS users were significantly less likely to experience dysmenorrhoea.

Local device problems

Expulsion and embedded device were the only outcomes for local device problems for which it was possible to extract data.

Expulsion. *Tables 29* and *30* show the summary expulsion rate ratios, and *Table 31* shows the single decrement life-table probability differences for the LNG-20 IUS compared with the non-hormonal IUDs.

LNG-20 IUS users were more likely to experience expulsion of the device than were IUD > 250 mm³ users (*Table 29*). The differences were only significant once follow-up had reached 5 years, when they showed an increase of over 50% in the expulsion rate of the LNG-20 IUS (rate ratio, 1.53; 95% CI, 1.13 to 2.07) and an absolute increase of over 4% in single decrement life-table probabilities (life-table difference, 4.4%; 95% CI, 1.46% to 7.34%).

The rate ratio indicated that women using the LNG-20 IUS were significantly less likely to have an expulsion after 2 years of use than were IUD ≤ 250 mm³ users (see *Table 30*) and there

TABLE 25 *Pregnancy: LNG-20 IUS (Mirena) compared with IUDs ≤ 250 mm³*

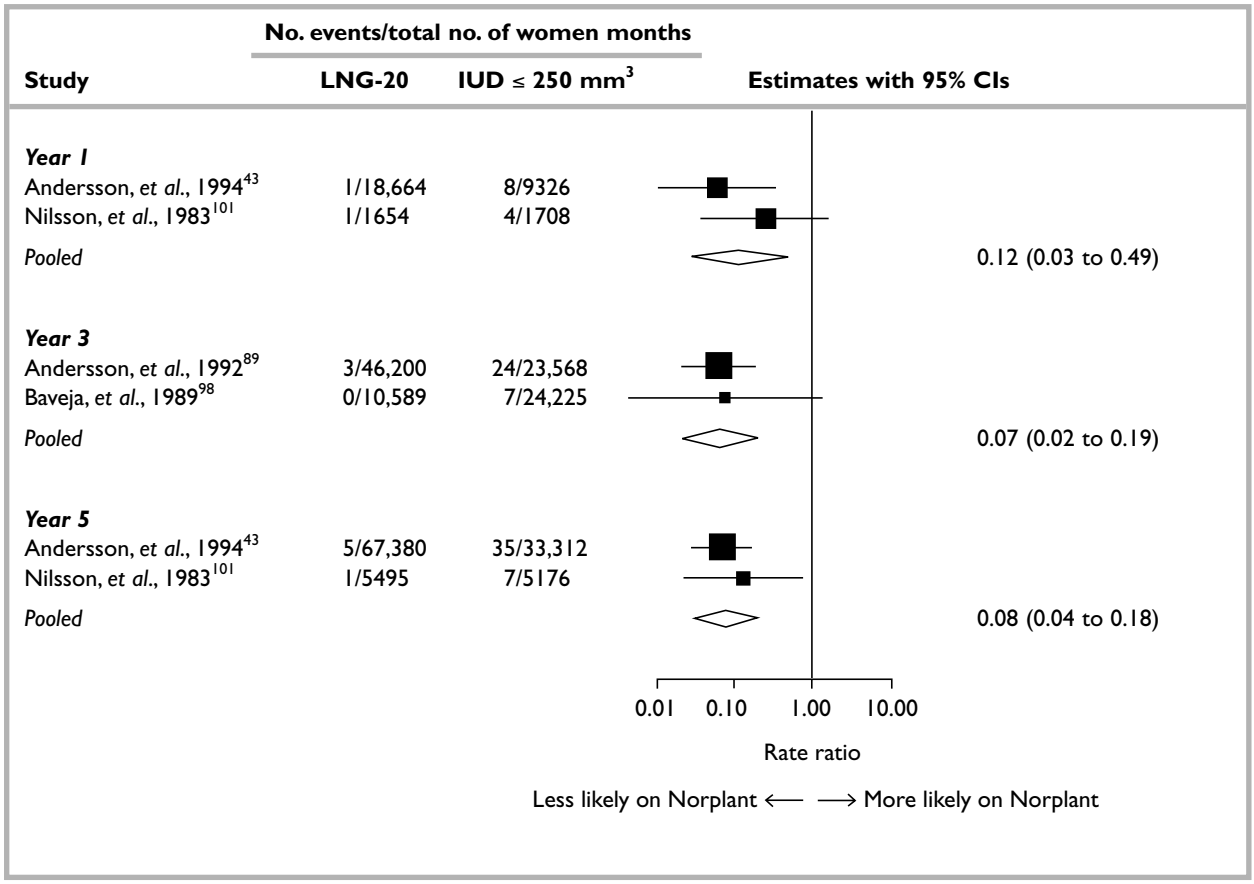


TABLE 26 *Pregnancy: LNG-20 IUS (Mirena) compared with LNG-30 IUS*

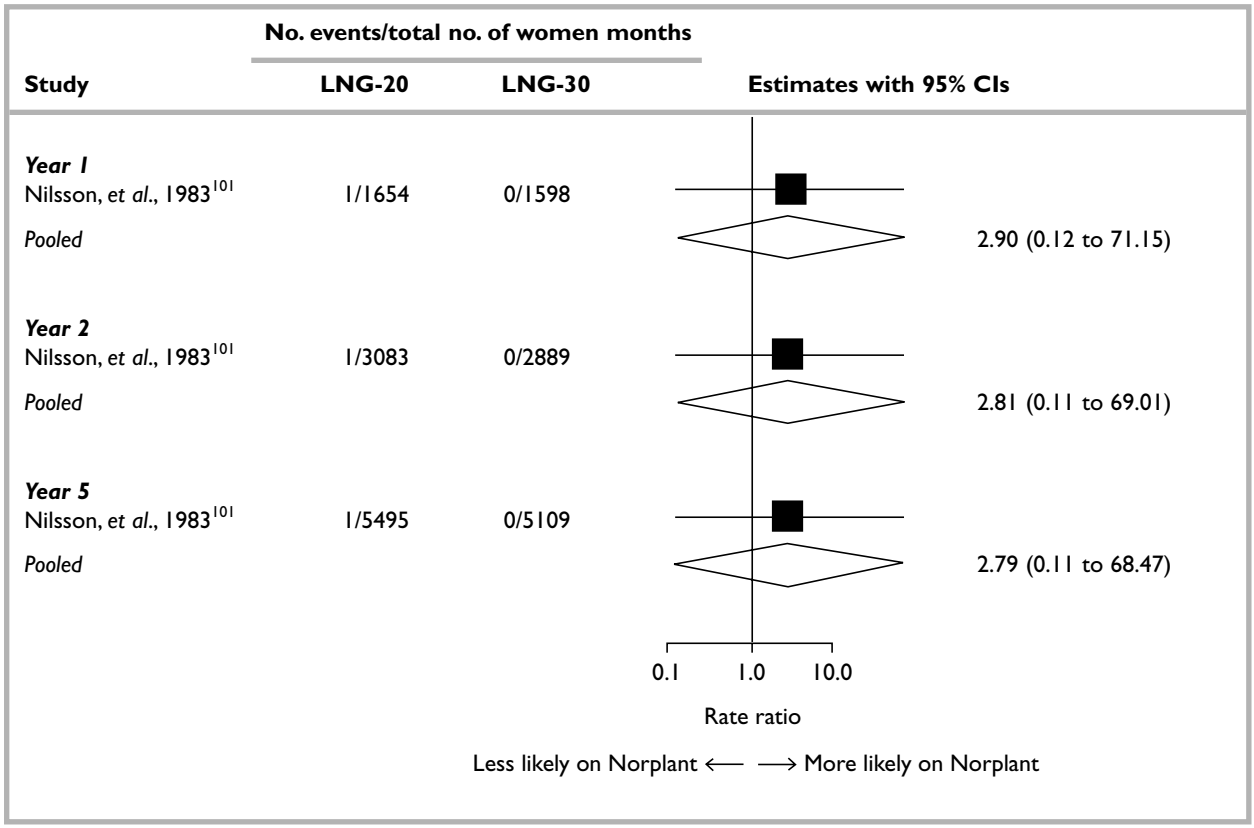
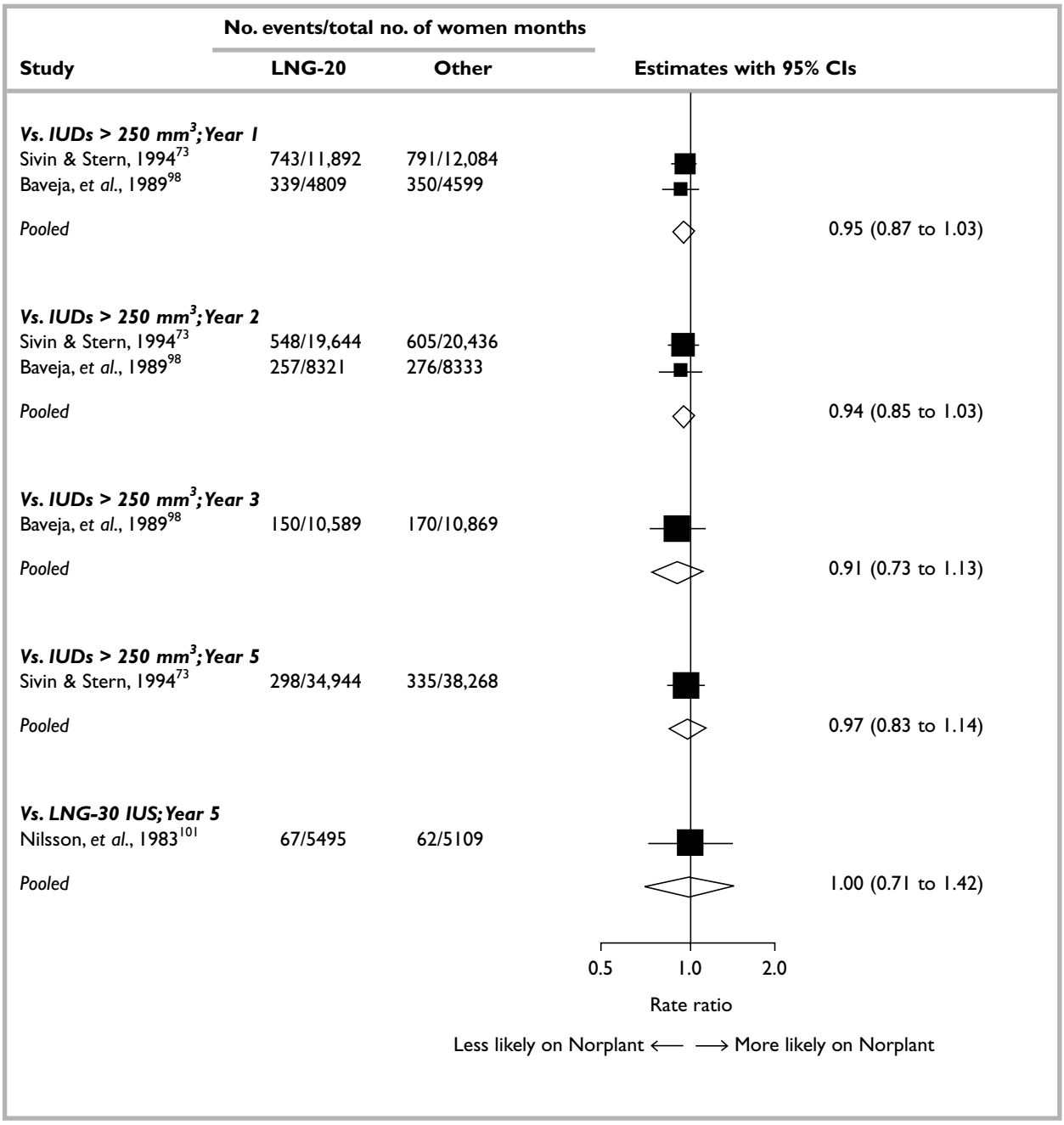


TABLE 27 *Continuation: LNG-20 IUS (Mirena) compared with IUDs > 250 mm³ and LNG-30 IUS*

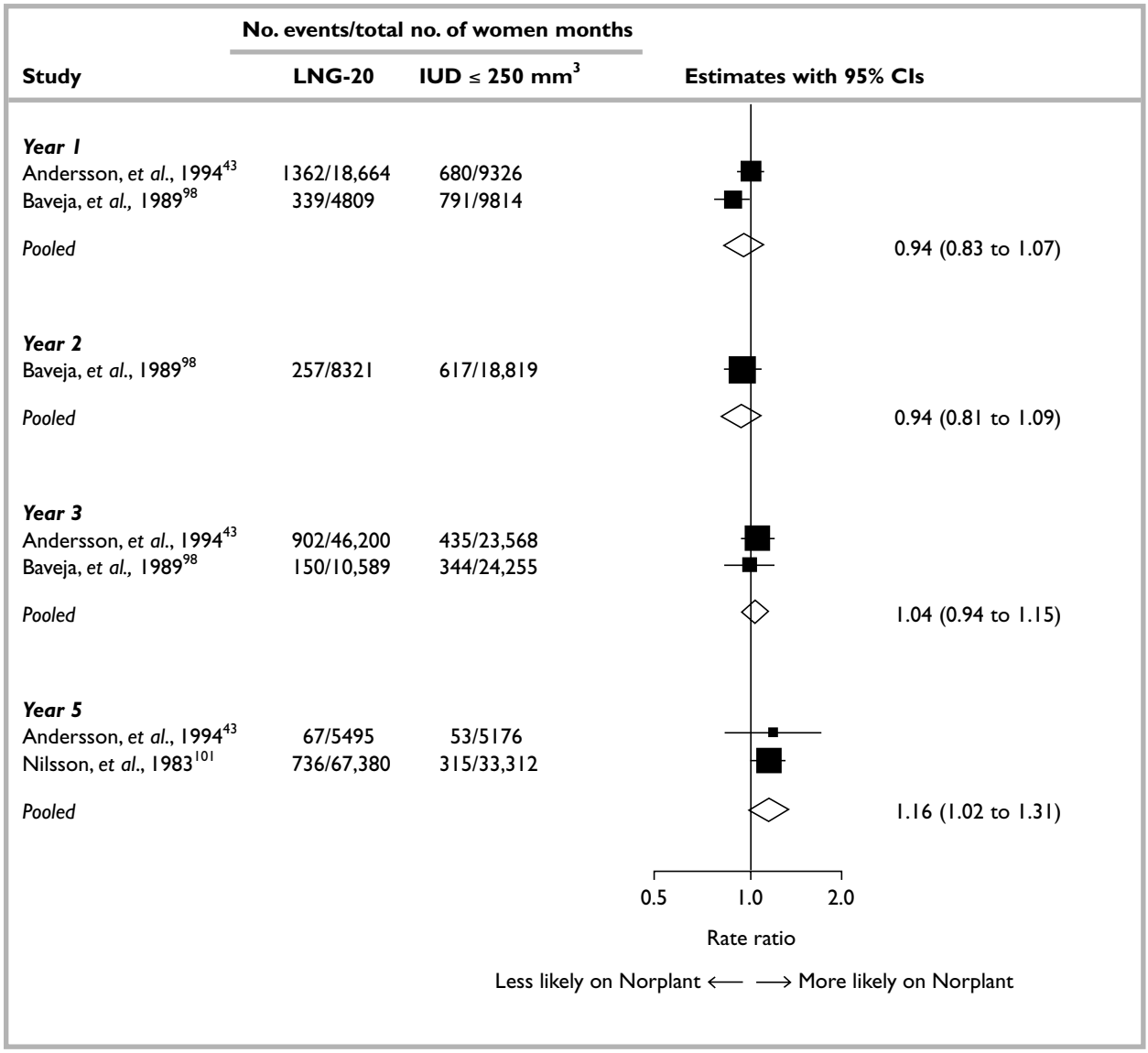


is a suggestion, albeit not statistically significant, that women using the LNG-20 IUS were less likely to have an expulsion after 1 and 3 years of use. Data collected on life-table probabilities suggested that LNG-20 IUS users were more likely to have an expulsion, although the difference is not significant (see *Table 31*). As data from different studies were used to determine the rate ratios and life-table probabilities, it was impossible to ascertain whether the difference in findings was due to the different methods of analysis or to the difference in the characteristics of the studies.

No significant difference was noticed in the rate of expulsion for the LNG-20 IUS and the higher dose LNG-30 IUS (*Table 29*), although the direction of the effect size suggests women using the lower dose IUS were less likely to experience an expulsion.

Embedment. There was one study, by Sivin and colleagues[73] which compared the LNG-20 IUS with the CuT 380Ag IUD, from which it was possible to extract data on the number of IUSs that become embedded. After 5 years follow-up, three IUSs had become embedded

TABLE 28 *Continuation: LNG-20 IUS (Mirena) compared with IUDs ≤ 250 mm³*



in 34,944 women months of LNG-20 IUS use and none of the IUDs had become embedded in 38,268 women months of use, giving a rate ratio of 7.00 (95% CI, 0.36 to 135.52).

Adverse events

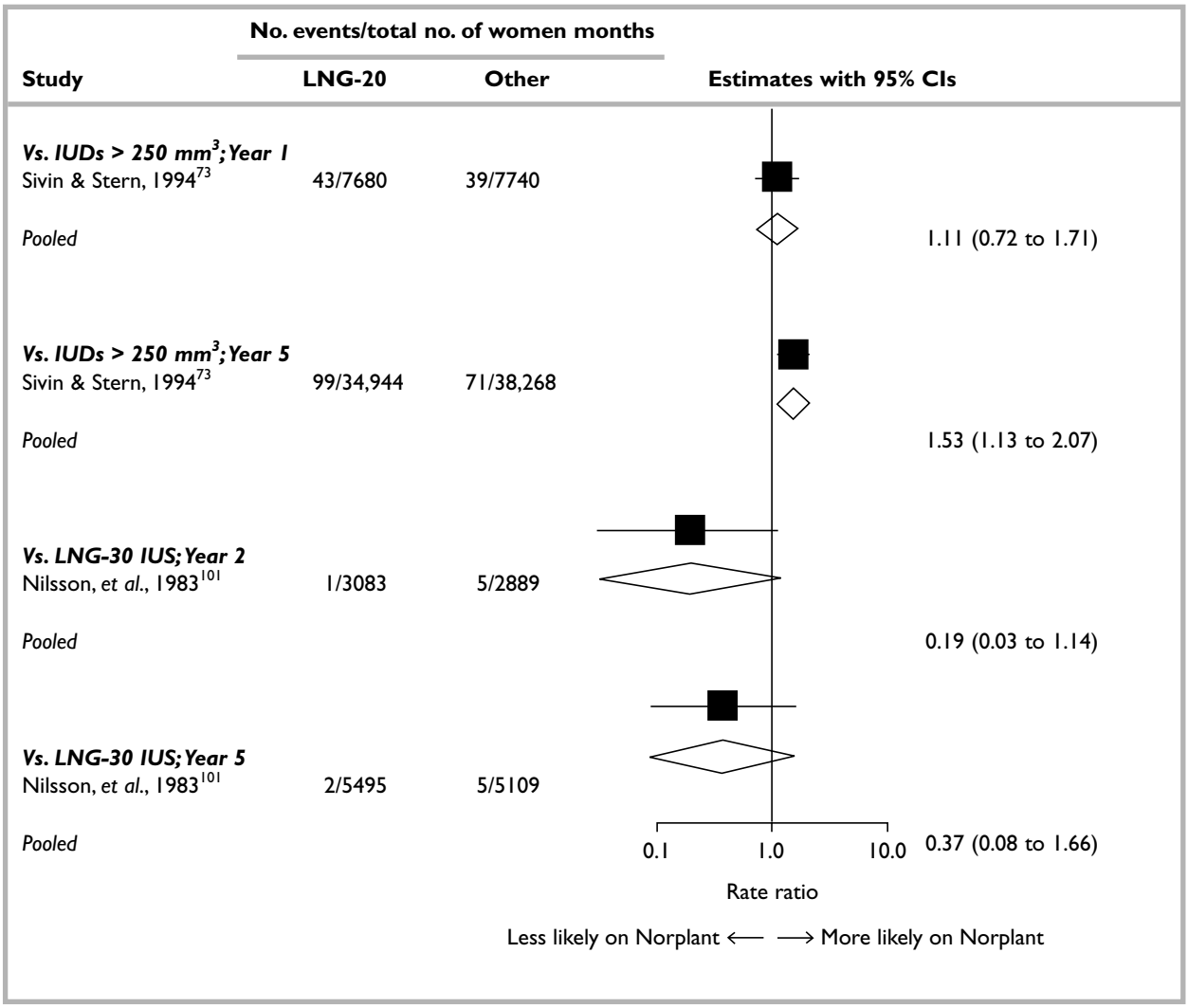
It was not possible to extract data on any adverse event outcomes, with the exception of ectopic pregnancies and PID.

Ectopic pregnancies. There was no evidence to suggest that the rate of ectopic pregnancy was significantly different in women using the LNG-20 IUS compared with those using the IUD > 250 mm³. There were no ectopic pregnancies in 34,944 women months of LNG-20 IUS use and two ectopic pregnancies in 38,268 women months of CuT 380Ag IUD use,[73] giving a rate ratio of 0.22 (95% CI, 0.01 to 4.56). No ectopic pregnancies had occurred in either group during the first 2 years of follow-up.

No significant differences were noted in the rate of ectopic pregnancy in LNG-20 IUS users compared with the rate in IUD ≤ 250 mm³ users after 1 year of use,[43,73] with a summary rate ratio of 0.72 (95% CI, 0.07 to 6.91). By years 3 and 5, significant differences were noted in the study by Andersson and colleagues,[43] with rate ratios of 0.1 (95% CI, 0.02 to 0.62) and 0.07 (95% CI, 0.01 to 0.41), respectively.

The rate ratio of ectopic pregnancy in LNG-20 IUS users compared with LNG-30 IUS users was 2.90 (95% CI, 0.12 to 71.15) at 1 year.[73]

TABLE 29 *Expulsion: LNG-20 IUS (Mirena) compared with IUDs > 250 mm³ and LNG-30 IUS*



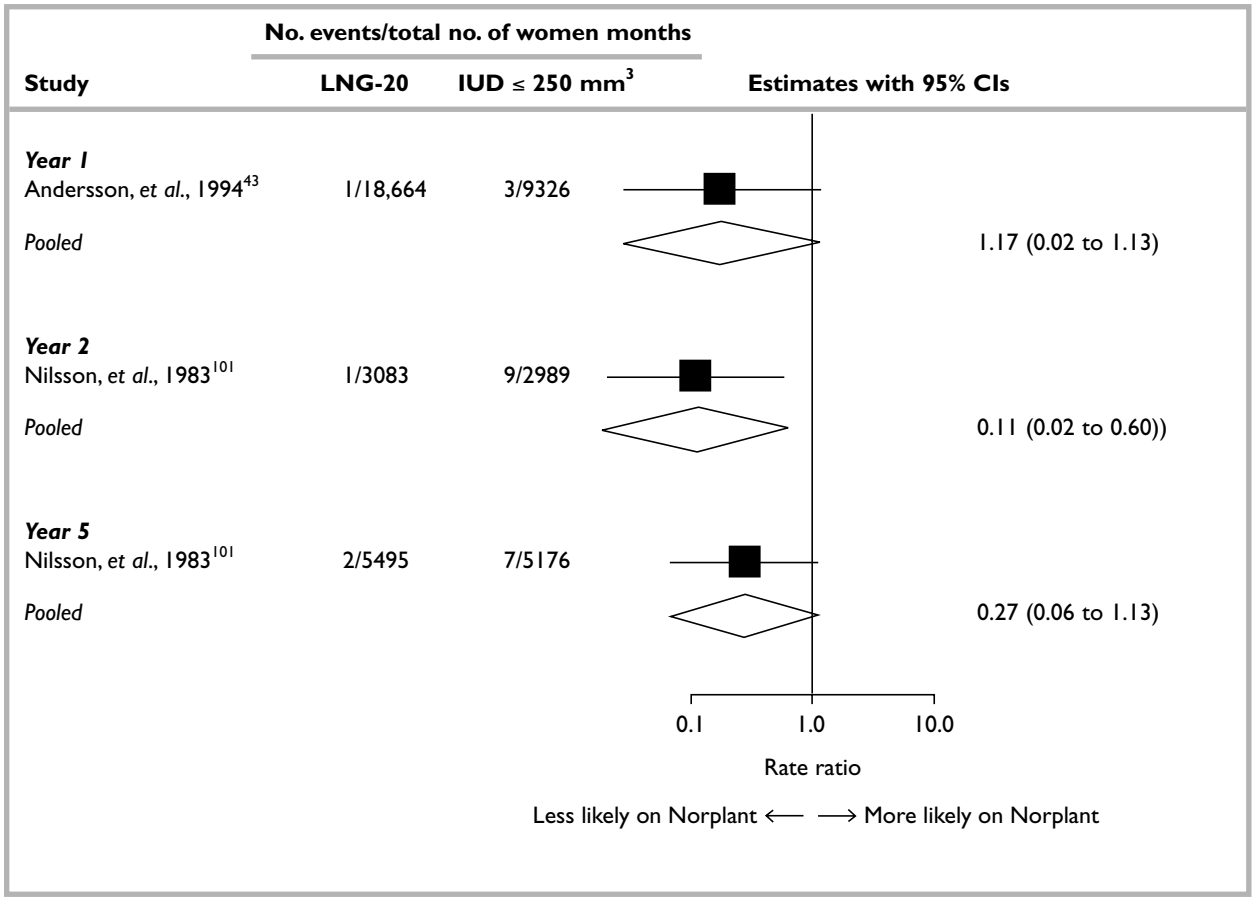
PID. No differences were found in the incidence of PID in LNG-20 IUS users when compared with the users of other investigated interventions. The study by Sivin and colleagues[73] reported ten cases of PID in LNG-20 IUS users after 7680 women months of use and eight cases in CuT 380Ag users in 7740 women months of use at 1 year follow-up, giving a rate ratio of 1.23 (95% CI, 0.50 to 3.03). Single decrement life-table probabilities provided by the authors were 1.6% (SE, ± 0.5) in LNG-20 IUS users in comparison with 1.3% (± 0.4) in the IUD users, with a difference of 0.3% (95% CI, –0.96% to 1.56%). In the study by Nilsson and colleagues,[101] at 2 years of follow-up there were no cases of PID in LNG-20 IUS users after 3083 women months of use, no cases in LNG-30 IUS users after 2889 women months of use and two cases in Nova-T IUD users after 2989 women months of use. The difference in rates between LNG-20 IUSs and Nova-T IUDs is not significant (0.15; 95% CI, 0.01 to 2.86). The study by Andersson and colleagues[43] did find that LNG-20 IUS users were significantly less likely to be diagnosed with PID than Nova-T IUD users, and that this difference was particularly so for younger women, but we were unable to use the data in the meta-analysis.

Reasons for discontinuation

Hormonal side-effects. *Table 32* shows the summary rate ratios for discontinuation of a contraceptive method due to hormonal side-effects (such as headaches, nausea or weight gain). After 5 years of follow-up LNG-20 IUS users were significantly more likely to discontinue because of hormonal side-effects than were any of the other IUD users. Heterogeneity was evident between results of the LNG-20 IUS and IUD ≤ 250 mm³ studies at year 3.

One study[73] provided single decrement life-table probabilities for discontinuation due to hormonal

TABLE 30 *Expulsion: LNG-20 IUS (Mirena) compared with IUDs ≤ 250 mm³*



side-effects and no difference was found between LNG-20 IUS users and IUD > 250 mm³ users at year 1, with an absolute reduction of –0.1% (95% CI, – 1.21% to 1.01%).

Menstrual disturbance. Data on menstrual disturbance as a reason for discontinuation of a method were extracted from two studies[73,98] that compared the LNG-20 IUS with IUDs > 250 mm³ and from two studies[98,101] that compared the LNG-20 IUS with IUDs ≤ 250 mm³.

Women using LNG-20 IUSs were significantly more likely to discontinue because of menstrual disturbance than were women using IUDs > 250 mm³: the rate ratios were 1.48 (95% CI, 1.02 to 2.14) at 1 year and 1.48 (95% CI, 1.23 to 1.79) at 5 years.[73] No difference in menstrual disturbance as a reason for discontinuation of method was evident between LNG-20 IUS users and IUD ≤ 250 mm³ users: the rate ratios were 1.18 (95% CI, 0.88 to 1.57) at 1 year and 1.17 (95% CI, 0.66 to 2.06) at 5 years.[101] There was no significant difference noted between LNG-20 and LNG-30 IUSs at year 1 follow-up (rate ratio, 0.5; 95% CI, 0.07 to 3.82).

A further breakdown shows that it is amenorrhoea, rather than bleeding and pain, which is more likely to be responsible for discontinuation of IUSs when compared with IUDs. After 1 year, the rate of discontinuation due to amenorrhoea was 65 times more likely in LNG-20 IUS users than in IUD > 250 mm³ users (rate ratio, 65.1; 95% CI, 4.01 to 109.84). By year 5, the rate ratio for discontinuation of LNG-20 IUS users compared with IUD > 250 mm³ users was 48.92 (95% CI, 16.93 to 141.36) for discontinuation due to amenorrhoea, and 0.71 (95% CI, 0.56 to 0.89) for discontinuation due to bleeding and pain.

A similar pattern was seen with the comparison of the LNG-20 IUS with IUDs ≤ 250 mm³, with the rate ratio at 5 years being 29.2 (95% CI, 1.75 to 488.04) for discontinuation due to amenorrhoea and 0.49 (95% CI, 0.24 to 1.01) for discontinuation due to bleeding and pain.

Significant differences were also apparent when the single decrement life-table probability differences were pooled in studies[73,98] that compared LNG-20 IUSs with IUDs > 250 mm³. There was

TABLE 31 *LNG-20 IUS compared with other IUDs: synthesis of single decrement life-table probabilities for expulsion*

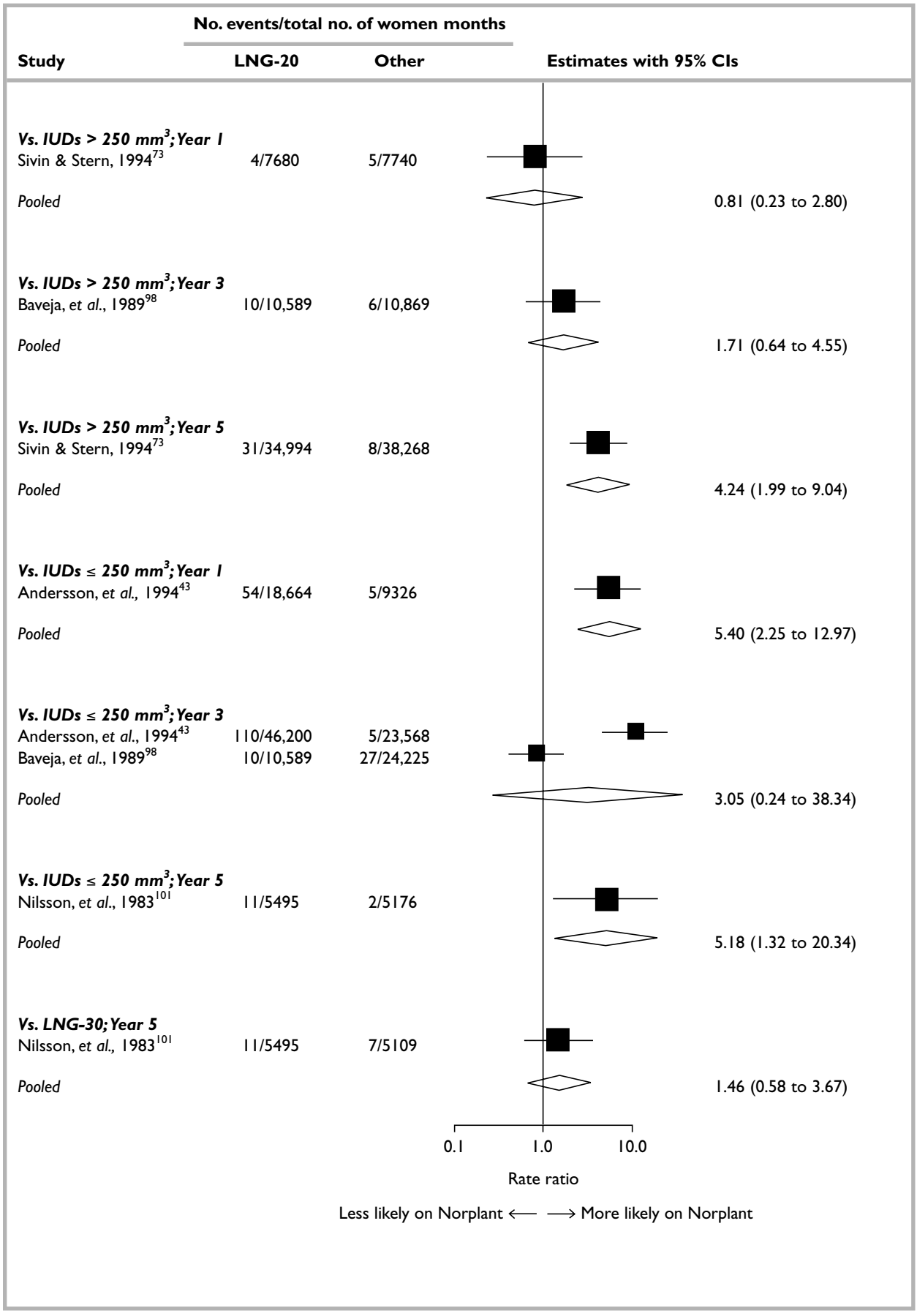
Follow-up period and studies	Single decrement life-table probability (± SE)		Measurement of true effect (± SE)
	LNG-20 IUS vs.	**IUD > 250 mm^3**	
Year 1			
Sivin & Stern, 1994[73]	6.4 (± 1.0)	5.8 (± 0.9)	0.6 (± 1.80)
Baveja, *et al.*, 1989[98]	6.5 (± 1.2)	5.3 (± 1.1)	1.2 (± 2.70)
			Summary, 0.84 (95% CI, –1.19 to 2.88)
Year 2			
Baveja, *et al.*, 1989[98]	9.2 (± 1.4)	7.1 (± 1.3)	2.1 (± 3.65)
			Summary, 2.1 (95% CI, –1.64 to 5.84)
Year 3			
Baveja, *et al.*, 1989[98]	10.6 (± 1.6)	7.4 (± 1.4)	3.0 (± 4.52)
			Summary, 3.0 (95% CI, –1.17 to 7.17
Year 5			
Sivin, & Stern, 1994[73]	11.8 (± 1.2)	7.4 (± 0.9)	4.4 (± 2.25)
			Summary, 4.4 (95% CI, 1.46 to 7.34)
	LNG-20 IUS vs.	**IUD ≤ 250 mm^3**	
Year 1			
Baveja, *et al.*, 1989[98*]	6.5 (± 1.2)	7.1 (± 1.2)	2.1 (± 3.40)
Baveja, *et al.*, 1989[98†]	9.2 (± 1.4)	7.7 (± 1.3)	1.5 (± 3.65)
			Summary, 1.65 (95% CI, –0.51 to 3.81)
Year 2			
Baveja, *et al.*, 1989[98*]	9.2 (± 1.4)	7.1 (± 1.2)	1.7 (± 2.44)
Baveja, *et al.*, 1989[98†]	9.2 (± 1.4)	7.7 (± 1.3)	1.6 (± 2.44)
			Summary, 1.81 (95% CI, –0.79 to 4.41)
Year 3			
Baveja, *et al.*, 1989[98*]	10.6 (± 1.6)	8.3 (± 1.3)	2.3 (± 4.52)
Baveja, *et al.*, 1989[86†]	10.6 (± 1.6)	8.5 (± 1.4)	2.1 (± 4.52)
			Summary, 2.2 (95% CI, –0.75 to 5.15)

* *Compared with CuT 220C IUD*
† *Compared with CuT 200B IUD*

an absolute increase in menstrual disturbance as a reason for discontinuation at 1 year of 6.91% (95% CI, 2.87% to 10.94%), at 2 years of 11.1% (95% CI, 6.26% to 15.94%) and at 3 years of 14.5% (95% CI, 8.78% to 20.22%). When focusing on amenorrhoea as the reason for discontinuation, the absolute increases in single decrement life-table differences were 5.04% (95% CI, 3.19% to 6.90%) at 1 year,[73,98] 13.3% (95% CI, 9.30% to 17.30%) at 2 years[98] and 19.3% (95% CI, 16.14% to 22.46%) at 5 years.[73] Other more detailed data on menstrual disturbance as a reason to discontinue were provided by Sivin and colleagues.[73] At year 1 no differences in absolute terms were observed between the LNG-20 IUS and the CuT 380Ag IUD for pain as a reason to discontinue (–0.9%; 95% CI, –2.86% to 1.06%). At 5 years LNG-20 IUS users were significantly less likely to discontinue because of bleeding and pain (single decrement life-table difference, –7.9%; 95% CI, –10.89% to –4.91%).

A similar pattern was seen in the comparison of LNG-20 IUSs with IUDs ≤ 250 mm^3. At 1 year there was an absolute increase in menstrual disturbance as the reason for discontinuation of 7.95% (95% CI, 5.14% to 10.76%) in LNG-20 IUS users, rising to 12.55% (95% CI, 9.05% to 16.05%) and 12.9%

TABLE 32 *Hormonal reasons for discontinuation: LNG-20 IUS (Mirena) compared with other methods*



(95% CI, 8.77% to 17.03%) at years 2 and 3, respectively.[98] Absolute increases for discontinuation due to amenorrhoea specifically were 5.07% (95% CI, 3.36% to 6.77%), 9.8% (95% CI, 7.54% to 12.06%), and 13.6% (95% CI, 10.8% to 16.41%) at years 1, 2 and 3, respectively. Unpublished data provided by Leiras (I Rauramo, Leiras Ltd: personal communication, 1999) on discontinuation because of amenorrhoea for the LNG-20 IUS compared with the Nova-T IUD in the study by Andersson and colleagues[43] demonstrated a huge variation between the participating centres, ranging from a multiple decrement probability of 2.7% in Finland to 19.6% in Hungary.

Other. No significant differences were noted between the LNG-20 IUS and the non-hormonal IUDs for other reasons for discontinuation. For discontinuation of method because of an adverse event, the rate ratios for the comparisons of the LNG-20 IUS with IUDs ≤ 250 mm^3 were 1.0 (95% CI, 0.59 to 1.68) after 1 year,[43] 1.14 (95% CI, 0.24 to 5.37) after 3 years,[98] and 0.78 (95% CI, 0.25 to 2.44) after 5 years.[101] The rate ratio for discontinuation due to adverse events in the comparison of the LNG-20 IUS with IUDs > 250 mm^3 was 1.03 (95% CI, 0.18 to 5.92) after 3 years.[98]

The rate ratios for planning a pregnancy as a reason for discontinuation of method were 0.94 (95% CI, 0.47 to 1.89) after 1 year and 1.11 (95% CI, 0.89 to 1.39) after 5 years in the comparison of the LNG-20 IUS with IUDs > 250 mm^3,[73] and 0.59 (95% CI, 0.27 to 1.28) after 5 years in the comparison of the LNG-20 IUS with IUDs ≤ 250 mm^3.[98] The rate ratios for personal reasons for discontinuation were 1.4 (95% CI, 0.69 to 2.81) and 1.12 (95% CI, 0.77 to 1.61) after 1 and 5 years, respectively, in the comparison of the LNG-20 IUS with IUDs > 250 mm^3.[73]

In addition, no difference in single decrement life-table probabilities was apparent for these outcomes in the one study that compared the LNG-20 IUS with the CuT 380Ag IUD.[73]

Progestasert

There were four intervention studies of Progestasert included in the meta-analysis. Three compared Progestasert with IUDs ≤ 250 mm^3 (two RCTs[111,116] and one non-RCT intervention[119]). The fourth study was an RCT comparison of Progestasert versus an inert IUD.[113] Follow-up for each of the studies was 1 year and all of the studies were conducted over 15 years ago.

Pregnancy

Table 33 shows that there was no significant difference between the contraceptive effectiveness of Progestasert and IUDs ≤ 250 mm^3.

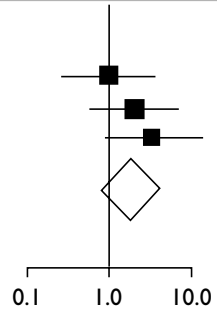
The rate of pregnancies was decreased by nearly 90% when Progestasert users were compared with users of inert IUDs (rate ratio, 0.09; 95% CI, 0.03 to 0.28).[113]

Continuation of method

The continuation of use of Progestasert and IUDs ≤ 250 mm^3 appeared similar at 1 year follow-up when rate ratios (1.03; 95% CI, 0.82 to 1.29) and

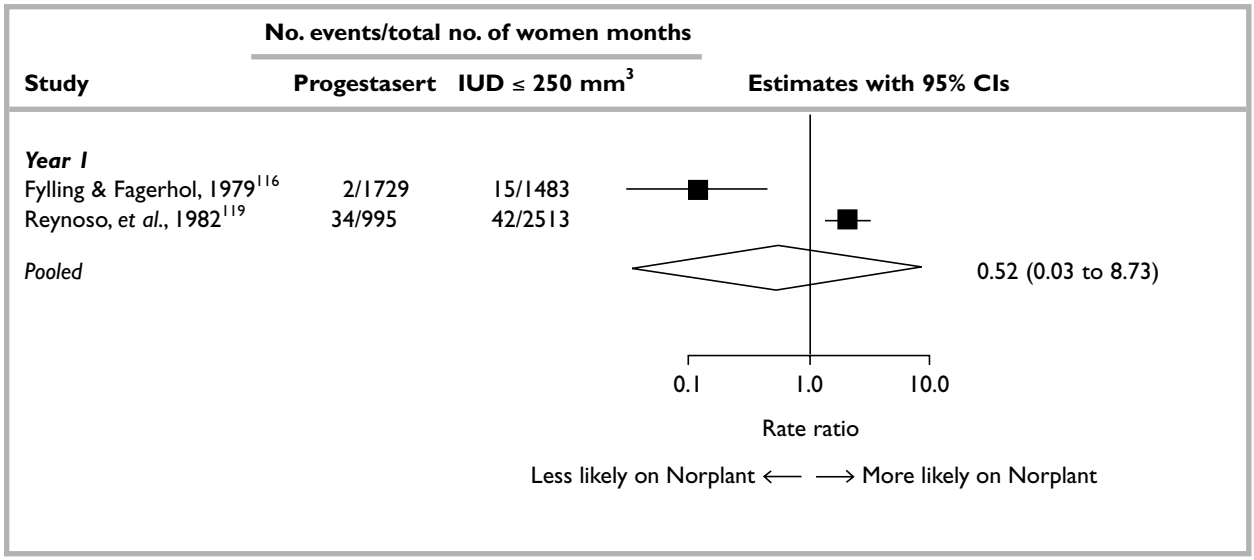
TABLE 33 *Pregnancy: Progestasert compared with IUDs ≤ 250 mm^3*

Study	No. events/total no. of women months: Progestasert	IUD ≤ 250 mm^3	Estimates with 95% CIs
Year 1			
Larsen, *et al.*, 1981[111]	4/1996	4/1943	
Fylling & Fagerhol, 1979[116]	7/1729	3/1483	
Reynoso, *et al.*, 1982[119]	4/995	3/2513	
Pooled			1.83 (0.85 to 3.92)



Less likely on Norplant ⟵ ⟶ More likely on Norplant

TABLE 34 *Expulsion: Progestasert compared with IUDs ≤ 250 mm³*



single decrement life-table probability differences 0.2% (95% CI, –8.5% to 8.9%) were calculated.[111] Data from the study by Newton and colleagues[113] indicated that Progestasert users were significantly more likely to continue with the method than were users of inert IUDs, giving a rate of ratio of 8.6 (95% CI, 1.37 to 15.83).

Rate of local device problems

The only outcome reported in this area was expulsion of device. No significant difference was found in the rate of expulsions when Progestasert was compared with IUDs ≤ 250 mm³ (*Table 34*) However, there is evidence of heterogeneity of results. When analysis is restricted to subgroup analysis of the results by RCTs only, Progestasert users were significantly less likely to experience expulsions (rate ratio, 0.11; 95% CI, 0.03 to 0.43), whereas non-RCTs showed that they were significantly more likely to experience them (rate ratio, 2.09; 95% CI, 1.44 to 3.02).

There was no association found between rate of expulsion for Progestasert users when compared with inert IUD users.

Rate of adverse events

It was only possible to extract data for ectopic pregnancy and PID outcomes. Combining the studies by Larsen and colleagues[111] and Fylling and colleagues,[114] there were three ectopic pregnancies in the Progestasert groups after 3725 women months of use and none in the IUDs ≤ 250 mm³ group after 3426 women months of use, giving a summary rate ratio of 3.57 (95% CI, 0.39 to 32.36).

There was no evidence to suggest a difference in the rate of PID between Progestasert users and users of inert IUDs (rate ratio, 0.29; 95% CI, 0.01 to 7.13).[113]

Reasons for discontinuation of method

In the comparisons of Progestasert with IUDs ≤ 250 mm³, the study by Fylling and colleagues[114] was the only one from which it was possible to extract reasons for discontinuation. The rate of discontinuation for menstrual bleeding and pain was three times higher in the Progestasert group (rate ratio, 3.0; 95% CI, 1.51 to 5.98).

There were no significant differences between intervention groups in the reasons for discontinuation in the study by Newton and colleagues[113] which compared Progestasert with the inert IUD. The rate ratios for discontinuation reasons were 1.15 (95% CI, 0.66 to 1.99) for menstrual disturbance, 1.29 (95% CI, 0.88 to 1.90) for planning pregnancy, and 0.46 (95% CI, 0.2 to 1.07) for other personal reasons.

Other

It was not possible to collect data for any of the hormonal side-effect or menstrual disturbance outcomes, or for pregnancy after removal of device.

Chapter 6

Further exploration of results

Further exploration of the findings of the meta-analysis was intended by the authors. This included investigating the impact of effect modifiers and study quality on results, and examining the extent to which publication bias had affected the results. As most of the summary effect sizes for outcomes were derived from data from a single study, not from the pooling of several studies, it was impossible to conduct any further exploration of the meta-analyses. The only exception to this was the subgroup analysis to assess the impact that study design had on the reporting of expulsions in the comparison of Progestasert users with IUD ≤ 250 mm^3 users (see chapter 5, page 52).

Chapter 7

Economic evaluation

Alternatives to be compared

Using the results of the systematic review and meta-analyses and the four criteria listed (see page 8) to determine the options to be compared in the economic evaluation, a number of comparisons were made. These are presented in *Table 35*.

Measuring effectiveness

The pregnancies averted by use of subdermal implants or IUSs relative to other contraceptive methods are presented in *Table 36*.

TABLE 35 *Alternatives compared in the economic evaluation*

Option (1)	compared with ...	Option (2)
Subdermal implants compared with other contraceptive methods		
Norplant	vs.	IUDs > 250 mm^3
Norplant	vs.	IUDs ≤ 250 mm^3
Norplant	vs.	Contraceptive pill
Norplant	vs.	DMPA
Hormone-impregnated IUSs compared with other contraceptive methods		
LNG-20 IUS	vs.	IUDs > 250 mm^3
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3

TABLE 36 *Pregnancies averted by subdermal implants or hormone-impregnated IUSs relative to other contraceptive methods*

Option (1)	compared with ...	Option (2)	Duration (years)	Estimated PR (2)*	Expected PR, RR†	PR (1)‡	AR§
Subdermal implants compared with other contraceptive methods							
Norplant	vs.	IUDs > 250 mm^3	1	0.00300	0.780	0.00234	0.00066
Norplant	vs.	IUDs > 250 mm^3	2	0.00700	0.550	0.00385	0.00315
Norplant	vs.	IUDs ≤ 250 mm^3	1	0.00800	0.102	0.00082	0.00718
Norplant	vs.	Contraceptive pill (perfect use‖)	1	0.00200	0.170	0.00034	0.00166
Norplant	vs.	Contraceptive pill (imperfect use‖)	1	0.01000	0.170	0.00170	0.00830
Norplant	vs.	DMPA	1	0.00100	1.000	0.00100	0.00000
Hormone-impregnated IUSs compared with other contraceptive methods							
LNG-20 IUS	vs.	IUDs > 250 mm^3	1	0.00300	1.010	0.00303	–0.00003
LNG-20 IUS	vs.	IUDs > 250 mm^3	2	0.00700	0.300	0.00210	0.00490
LNG-20 IUS	vs.	IUDs > 250 mm^3	3	0.01000	0.110	0.00110	0.00890
LNG-20 IUS	vs.	IUDs > 250 mm^3	5	0.01400	0.660	0.00924	0.00476
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3	1	0.00800	0.120	0.00096	0.00704
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3	3	0.05700	0.070	0.00399	0.05301

* *Pregnancy rates (PRs) with Option (2) per user across the duration stated*
† *Relative risk (RR) of pregnancy (pregnancy rate ratio) with Option (1) compared with Option (2)*
‡ *Estimated pregnancy rate with Option (1) per user across the duration stated = PR (2) x RR*
§ *Pregnancies averted = attributable risk (AR) of pregnancy (pregnancy rate difference) with Option (2) compared with Option (1)*
‖ *Perfect use of a contraceptive method is defined as both consistent and correct use of the method from its initiation, and imperfect use is inconsistent or incorrect use of the method at any time from its initiation*

Generally the number of pregnancies averted per user by subdermal implants or IUSs relative to other contraceptive methods is positive when the difference between estimated pregnancy rate and expected pregnancy rate is calculated. This implies that subdermal implants and IUSs are generally more effective at preventing pregnancies than are other contraceptive methods. These differences are generally only marginal. For Norplant compared with DMPA for a duration of 1 year, the difference in pregnancies averted per user is zero. This implies that these contraceptive methods are equally effective at preventing pregnancies, although it was not possible to determine the relative effectiveness in the meta-analysis as there were no pregnancies among women in either intervention group. For the LNG-20 IUS compared with IUDs > 250 mm^3 for a duration of therapy of 1 year the difference in the number of pregnancies averted per user is negative. This implies that IUDs > 250 mm^3 are more effective at preventing pregnancies than the LNG-20 IUS across this time period, when the difference between estimated and expected pregnancy rate is calculated.

Measuring costs

The net ingredient cost for each contraceptive method included in the economic evaluation was as follows: Norplant, £179; LNG-20 IUS (Mirena), £99; IUD ≤ 250 mm^3, £10; IUD > 250 mm^3, £10; DMPA, £18; contraceptive pill, £4 (low cost) and £36 (high cost). A high and low net ingredient cost for the contraceptive pill is used to reflect the range of prices charged for different brands currently available.

The incremental costs of subdermal implants and IUSs relative to other contraceptive methods are presented in *Table 37*. As shown in *Table 36*, the same contraceptive method over the same duration of follow-up may be found to have a slightly different effect on preventing pregnancies. This is due to underlying differences in the clinical trials on which the systematic review and meta-analyses were based. These differences have an impact on the calculation of the cost of each contraceptive method, a component of which is the cost of unplanned pregnancies (estimated as the probability of an unplanned pregnancy

TABLE 37 *Incremental costs of subdermal implants or hormone impregnated IUSs relative to other contraceptive methods*

Option (1)	compared with ...	Option (2)	Duration (years)	Cost, £ (1)*	Cost, £ (2)†	Incremental cost, £‡
Subdermal implants compared with other contraceptive methods						
Norplant	vs.	IUDs > 250 mm^3	1	307	138	168
Norplant	vs.	IUDs > 250 mm^3	2	338	172	166
Norplant	vs.	IUDs ≤ 250 mm^3	1	305	143	162
Norplant	vs.	Contraceptive pill (perfect use, low cost)	1	305	132	173
Norplant	vs.	Contraceptive pill (perfect use, high cost)	1	305	163	142
Norplant	vs.	Contraceptive pill (imperfect use, low cost)	1	306	139	167
Norplant	vs.	Contraceptive pill (imperfect use, high cost)	1	306	171	135
Norplant	vs.	DMPA	1	305	145	161
Hormone-impregnated IUSs compared with other contraceptive methods						
LNG-20 IUS	vs.	IUDs > 250 mm^3	1	227	138	89
LNG-20 IUS	vs.	IUDs > 250 mm^3	2	256	172	84
LNG-20 IUS	vs.	IUDs > 250 mm^3	3	283	202	80
LNG-20 IUS	vs.	IUDs > 250 mm^3	5	342	257	84
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3	1	225	143	82
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3	3	286	248	39

* *Net ingredient costs + dispensing costs + costs of GP and FPC + expected costs of unplanned pregnancies for Option (1) across the duration stated*
† *Net ingredient costs + dispensing costs + costs of GP and FPC + expected costs of unplanned pregnancies for Option (2) across the duration stated*
‡ *Cost (1) – Cost (2)*

multiplied by the cost of that pregnancy). This explains why the same contraceptive method used for the same duration may have a different cost attached to it in *Table 37*.

The incremental costs of subdermal implants and IUSs relative to other contraceptive methods are positive in all instances. This implies that subdermal implants and IUSs are more expensive than other contraceptive methods across the various time periods considered. For subdermal implants relative to other contraceptive methods this additional cost ranges from £135 to £173. For IUSs relative to other contraceptive methods this additional cost ranges from £39 to £89.

Measuring cost-effectiveness

The incremental costs per pregnancy averted of subdermal implants or IUSs relative to other contraceptive methods are presented in *Table 38*.

For subdermal implants relative to other contraceptive methods, where a cost-effectiveness ratio is calculated, incremental costs per pregnancy averted range from £16,285 to £255,102. For example, this indicates that for Norplant compared with IUDs ≤ 250 mm^3 for a duration of 1 year, it would cost an extra £22,566 to prevent an extra pregnancy by changing the contraceptive method to Norplant from the IUD ≤ 250 mm^3. For Norplant compared with DMPA injections for a duration of 1 year, DMPA injections are shown to 'dominate' Norplant. In this instance, this means that DMPA injections are equally as effective as Norplant at preventing pregnancies across the time period considered and are also less costly.

For IUSs relative to other contraceptive methods, where a cost-effectiveness ratio is calculated, incremental costs per pregnancy averted range from £721 to £17,739. For the LNG-20 IUS compared with the IUD > 250 mm^3 for a duration of 1 year, the IUD > 250 mm^3 is shown to dominate the LNG-20 IUS. In this instance, this means that the IUD > 250 mm^3 is more effective than the LNG-20 IUS at preventing pregnancies across the time period considered and is also less costly.

TABLE 38 *The incremental costs per pregnancy averted of subdermal implants or hormone-impregnated IUSs relative to other contraceptive methods*

Option (1)	compared with ...	Option (2)	Duration (years)	Incremental cost(£)*	AR†	Incremental cost/ pregnancy averted (£)‡
Subdermal implants compared with other contraceptive methods						
Norplant	vs.	IUDs > 250 mm^3	1	168	0.00066	255,102
Norplant	vs.	IUDs > 250 mm^3	2	166	0.00315	52,692
Norplant	vs.	IUDs ≤ 250 mm^3	1	162	0.00718	22,566
Norplant	vs.	Contraceptive pill (perfect use, low cost)	1	173	0.00166	104,198
Norplant	vs.	Contraceptive pill (perfect use, high cost)	1	142		85,258
Norplant	vs.	Contraceptive pill (imperfect use, low cost)	1	167	0.00830	20,073
Norplant	vs.	Contraceptive pill (imperfect use, high cost)	1	135		16,285
Norplant	vs.	DMPA	1	161	0.00000	DOM§
Hormone-impregnated IUSs compared with other contraceptive methods						
LNG-20 IUS	vs.	IUDs > 250 mm^3	1	89	–0.00003	DOM§
LNG-20 IUS	vs.	IUDs > 250 mm^3	2	84	0.00490	17,205
LNG-20 IUS	vs.	IUDs > 250 mm^3	3	80	0.00890	9042
LNG-20 IUS	vs.	IUDs > 250 mm^3	5	84	0.00476	17,739
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3	1	82	0.00704	11,684
LNG-20 IUS	vs.	IUDs ≤ 250 mm^3	3	39	0.05301	721

* *Incremental cost of Option (1) relative to Option (2) over the duration stated*
† *Pregnancies averted = AR of pregnancy (pregnancy rate difference) with Option (2) compared with Option (1)*
‡ *Incremental cost/pregnancies averted*
§ *DOM = 'dominates' = Option (2) is less costly and equally or more effective than Option (1)*

TABLE 39 *Results of sensitivity analysis: using lower and upper CI limits*

Option (1)	compared with ...	Option (2)	Duration (years)	Incremental cost per pregnancy averted (£)		
				Baseline	Lower CI limit on RR*	Upper CI limit on RR†
Subdermal implants compared with other contraceptive methods						
Norplant	vs.	IUDs > 250 mm^3	1	255,102	61,634	DOM‡
Norplant	vs.	IUD > 250 mm^3	2	52,692	26,168	DOM‡
Norplant	vs.	IUD ≤ 250 mm^3	1	22,566	20,380	DOM‡
Norplant	vs.	Contraceptive pill (perfect use, low cost)	1	104,198	88,103	DOM‡
Norplant	vs.	Contraceptive pill (perfect use, high cost)	1	85,258	72,062	DOM‡
Norplant	vs.	Contraceptive pill (imperfect use, low cost)	1	20,073	16,854	DOM‡
Norplant	vs.	Contraceptive pill (imperfect use, high cost)	1	16,285	13,646	DOM‡
Hormone-impregnated IUSs compared with other contraceptive methods						
LNG-20 IUS	vs.	IUD > 250 mm^3	1	DOM‡	34,785	DOM‡
LNG-20 IUS	vs.	IUD > 250 mm^3	2	17,205	12,713	DOM‡
LNG-20 IUS	vs.	IUD > 250 mm^3	3	9042	8031	DOM‡
LNG-20 IUS	vs.	IUD > 250 mm^3	5	17,739	7518	DOM‡
LNG-20 IUS	vs.	IUD ≤ 250 mm^3	1	11,684	10,511	20,855
LNG-20 IUS	vs.	IUD ≤ 250 mm^3	3	721	635	969

* *Incremental cost per pregnancy averted calculated using lower 95% CI on RR of pregnancy with Option (1) compared with Option (2)*
† *Incremental cost per pregnancy averted calculated using upper 95% CI on RR of pregnancy with Option (1) compared with Option (2)*
‡ *DOM = 'dominates' = Option (2) is less costly and equally or more effective than Option (1)*

The cost-effectiveness ratio for the LNG-20 IUS relative to the IUD > 250 mm^3 for a duration of 3 years (£9042 per pregnancy averted) is lower than the cost-effectiveness ratio for 2 years and 5 years of protection. This may be because 3 years is the optimum time period for the LNG-20 IUS relative to the IUD > 250 mm^3 in terms of cost-effectiveness (i.e. this difference reflects the true variability in cost-effectiveness over time) or it may simply be due to underlying differences in the clinical trials on which the systematic review and meta-analyses are based. We believe that the latter is more likely to be the case, and that the lower cost-effectiveness ratio is caused by methodological differences in the different studies pooled in the meta-analyses to generate data for the cost-effectiveness analysis.

Sensitivity analysis

The results of the sensitivity analysis carried out using the lower and upper 95% CIs of the rate ratios are presented in *Table 39*.

The cost-effectiveness ratios using lower and upper CIs are of the expected magnitude relative to baseline levels. The incremental costs per pregnancy averted when the lower 95% CIs of the pregnancy rate ratios are used ranged from £13,646 to £88,103 for subdermal implants relative to other contraceptive methods and from £635 to £34,785 for IUSs relative to other contraceptive methods. When the upper limits of the 95% CIs of the pregnancy rate ratios are used, with the exception of the comparison between the LNG-20 IUS and IUDs ≤ 250 mm^3, other contraceptive methods are found to be less costly and equally or more effective than subdermal implants or IUSs in terms of preventing pregnancy across the time period.

Table 40 shows the results of the sensitivity analysis when the pregnancy rates (for contraceptive methods other than subdermal implants or IUSs – i.e. 'Option 2') that were estimated by the Steering Group are replaced by those provided by Trussell and Kost.[15]

TABLE 40 *Results of the sensitivity analysis: using contraceptive failure rates after 1 year of use provided by Trussell and colleagues*

Option (1)	compared with ...	Option (2)	PR using Trussell estimates	AR	Incremental cost (£)	Incremental cost per pregnancy averted (£)
Subdermal implants compared with other contraceptive methods						
Norplant	vs.	IUD ≤ 250 mm^3	0.02	0.01796	150	8129
Norplant	vs.	Contraceptive pill (low cost)	0.03	0.0249	146	5823
Norplant	vs.	Contraceptive pill (high cost)	0.03	0.0249	145	6345
Norplant	vs.	DMPA	0.003	0	158	DOM*
Hormone-impregnated IUSs compared with other contraceptive methods						
LNG-20 IUS	vs.	IUD ≤ 250 mm^3	0.02	0.0176	71	466

* *DOM = 'dominates' = Option (2) is less costly and equally or more effective than Option (1)*

When the Trussell and Kost estimates are used, the incremental costs per pregnancy averted for Norplant relative to the contraceptive pill (low cost), the contraceptive pill (high cost) and the IUD ≤ 250 mm^3 are £5823, £6345 and £8129, respectively, after 1 year of use. DMPA injections are found to be less costly and equally or more effective than Norplant over a 1-year period. In this analysis, the incremental cost per pregnancy averted for the LNG-20 IUS relative to the IUD ≤ 250 mm^3 is £466 after 1 year.

Chapter 8
Discussion

Despite the extensive research that has been conducted to determine the efficacy and effectiveness of both subdermal contraceptive implants and IUSs in comparative studies, only limited data could be extracted from the numerous studies identified. The majority of studies were either poorly designed, lacked clarity when reporting outcomes or measuring outcomes, or focused on interventions that are unlikely to be of interest to either patients or policy makers.

Types of investigated interventions

Subdermal implants

The majority of the subdermal implant studies included in the review were comparisons of different types of implants rather than studies comparing implants with other contraceptive methods. While some of these comparisons may provide useful information to policy makers and providers of family planning services, they are not necessarily informative to the contraceptive user, who wants to decide which of the different contraceptive methods to use. The non-randomised studies compared implants with a broader spectrum of methods, but the design of these studies makes the results subject to bias.

IUSs

The studies comparing IUSs with different contraceptive methods were less varied, either being studies of IUSs releasing different progestogen doses or studies comparing IUSs with IUDs. There was only one study that compared IUSs with subdermal implants, despite the likely similarity in the demographic characteristics of women choosing either of these methods. There were no studies comparing IUSs with contraceptive methods that are more reliant on user compliance, such as oral contraceptives or DMPA injections.

Effectiveness

Subdermal implants

The comparative studies with subdermal implants included in the meta-analysis demonstrated that they were effective methods for preventing unwanted pregnancy, with only five pregnancies in 4637 women years of follow-up in women using Norplant, two in 2191 women years of follow-up in women using Norplant-2 and none in 1752 women years of follow-up in those using Implanon. **However, there was insufficient evidence from the comparative studies included in this systematic review to suggest that (a) one type of subdermal implant was more effective in preventing unwanted pregnancy than another or (b) implants were any more or less effective than the contraceptive methods with which they were compared.**

In 1992, the elastomer used in Norplant was changed.[129] Before 1992, the pregnancy rate in women weighing 70 kg or more was higher than the rate in lighter women and it is believed that the change in the elastomer has rectified this. Because of the limited number of studies included in the meta-analysis of pregnancy outcomes it was not possible to do a subgroup analysis of studies carried out before 1992 and compare the results with those from studies starting after 1992 to see if the change in elastomer had an effect on pregnancy outcomes.

Intrauterine systems

There was insufficient evidence to indicate a difference in the pregnancy rates between LNG-20 IUS users and IUD > 250 mm^3 users. LNG-20 IUS users were significantly less likely to experience both intrauterine and extrauterine pregnancies than IUD ≤ 250 mm^3 users when summary rate ratios were calculated. A significant difference was not observed when single decrement life-table probabilities were calculated for unplanned pregnancy. The reason no significance was observed with the life-table difference could be due to lack of power as the data were extracted from a single study, in which, in fact, no significant difference was seen in the rate ratios either.

Explaining the lack of difference in effectiveness results

There may, in fact, be no difference in effectiveness between the contraceptive methods compared, but there are insufficient data included in the meta-analyses to conclude this. However, these studies could have failed to detect a real

difference in the relative effectiveness of the methods compared for the following reasons. These findings may not reflect usage in the real world. The 'default state' of implants is likely to make user failure far less likely than with other contraceptive methods. In the main, comparisons were of contraceptive methods with similar default states rather than comparisons of subdermal implants or IUSs with methods for which user adherence, particularly in some groups such as adolescents, is likely to be a factor in effectiveness. The failure to detect a difference in contraceptive effectiveness between methods may be due to the small number of women enrolled and followed in these studies – that is there is inadequate power to detect clinically important differences in effectiveness (see *Table 41*). This was also reflected by the very wide CIs around most of the calculated rate ratios. For example, to detect a two-fold increase in the effectiveness of implants relative to oral contraceptives in preventing unwanted pregnancy (where the pregnancy rate of oral contraceptive combined pill users is assumed to be 0.1% per annum with perfect use) with 80% power at 5% significance, it would be necessary to recruit over 50,000 women to each arm of the trial. As further comparative data become available on the effectiveness of subdermal implants and IUSs, for example from studies such as the ongoing World Health Organization (WHO) multicentre trials of LNG-20 IUS versus the CuT 380A IUD,[86] it will be interesting to see what impact these have on the summary effect size for effectiveness outcomes.

Women who agree to be part of a contraceptive study are not likely to be representative of the general population of female contraceptive users.

TABLE 41 *Sample size calculations to determine the number of women needed in contraceptive effectiveness trials comparing implantable contraceptives with other reversible contraceptives to ensure adequate power*[*]

Compared contraceptive methods (control)	Percentage of women experiencing unplanned pregnancy using comparative[†]	Sample size required in each arm of the study	Total no. of women recruited (to date) in comparative studies that were included in meta-analyses	
			Intervention	Control
Subdermal implants (intervention)				
Progestin only pill	0.5	10,166	120	117
Combined pill	0.1	50,978	50	101
Condom	3	1644	0	0
Spermicides	6	814	0	0
Cap: parous women	26	160	0	0
Cap: nulliparous women	9	530	0	0
CuT IUD > 250 mm^3	0.6	8466	370	222
CuT IUD ≤ 250 mm^3	1	5065	371	497
Progestasert IUD	1.5	3364	0	0
LNG-20 IUS	0.1	50,978	0	0
DMPA	0.3	1558	50	22
LNG-20 IUS (intervention)				
Progestin only pill	0.5	10,166	0	0
Combined pill	0.1	50,978	0	0
Condom	3	1644	0	0
Spermicides	6	814	0	0
Cap: parous women	26	160	0	0
Cap: nulliparous women	9	530	0	0
CuT IUD > 250 mm^3	0.6	8466	1600	1555
CuT IUD ≤ 250 mm^3	1	5065	2460	2524
Progestasert IUD	1.5	3364	0	0
Norplant	0.1	50,978	0	0
DMPA	0.3	1558	0	0

[*] *The sample sizes have been calculated to detect a two-fold increase in the effectiveness of implantable contraceptives relative to the other reversible contraceptive methods, with 80% power at 5% significance*

[†] *Contraceptive failure rates within first year of use provided by Trussel and colleagues. Assume perfect use (i.e. consistent and correct use from initiation of contraceptive method)*

They are more likely to be motivated and able to commit to continued follow-up. Importantly, women who are prepared to be randomised are not likely to be representative since user choice of contraceptive method is related to effectiveness.[13]

Factors influencing effectiveness results

The risk of pregnancy may vary dramatically between different populations of women. However, the relative effectiveness of the contraceptive methods would not be altered by these factors if the women were randomised to method. In the non-RCT studies, factors such as use of additional contraceptive methods, frequency of sexual activity, age, nutritional status and motivation to avoid pregnancy will have an impact on the risk of contraceptive failure. In addition, consideration must be paid to the fecundity of a population. Some studies only include parous women to take account of this problem. Although the age range of women enrolled in both the RCTs and non-RCT comparative studies was wide, generally the women had had a previous pregnancy and/or birth. In studies in which parity was variable, the number of women who had never had a pregnancy was usually very small. Even in the studies confined to adolescent women, parity was high. In the case of subdermal implants, the non-RCT comparisons provided some insight into how women who chose these methods differed from women who chose alternatives. In general, implant users were older, had a higher parity and were more likely to have tried other methods of contraception. All of these factors are likely to affect a woman's motivation to continue with the method. For example, if women are using implants as a way of birth spacing, or indeed have completed their family and do not want any more children, their motivation to continue with the method will be high. Among adolescents using implants there may be other factors which influence motivation to use contraceptives, such as social pressures not to have a further pregnancy. In addition, the adolescent women using implants tended to be from inner city settings and have low socio-economic status. It is therefore inappropriate to generalise the results from these studies to adolescents as a whole. Again, it was not possible to do any subgroup analysis to investigate the impact of factors such as age and parity.

Other factors such as whether women are breastfeeding or are using additional contraceptive methods are likely to influence effectiveness results. In one study,[66] adolescents were advised to use condoms, as well as the oral contraceptive pill or Norplant, to provide protection from sexually transmitted infections. In that study there were no significant differences between the intervention groups in frequency of condom use. However, differences in condom use could affect the apparent contraceptive efficacy of methods being compared in this study.

Rate of pregnancy after discontinuation of method

Although subdermal implants and IUSs are seen as more 'permanent' methods, their protective effect is soon reversed and there was no difference in pregnancy rates after discontinuation in comparison with other contraceptive methods, although the numbers followed up were small.

Acceptability

Continuation and reasons for discontinuation

Although it is very useful to know how many unwanted pregnancies a method prevents, this information is of little value without collecting data on outcomes which reflect the acceptability of a method. A method may be efficacious in terms of preventing unwanted pregnancy, but if the method is discontinued within a short time its value as a method of contraception is greatly reduced. The results of the meta-analyses indicated that women using Norplant were around twice as likely to continue with this method in comparison with women using the pill, vaginal rings or DMPA injections. However, women using the LNG-20 IUS were significantly less likely to continue when compared with women using IUDs > 250 mm^3. When considering the issue of effectiveness, information on continuation and reasons for discontinuation need to be collected as these outcomes are likely to reflect the acceptability of a contraceptive method. In addition, women who discontinue with a contraceptive method may become unintentionally pregnant before starting another method.

Another issue that must be considered when focusing on acceptability and the generalisability of the results is the cultural setting in which the trials included in the reviews were conducted. For example, women from different backgrounds may view menstrual changes differently. Some women may view amenorrhoea resulting from using a contraceptive method as an advantage, whereas for others it is the primary reason for

the discontinuation of that method. Certainly the Implanon versus Norplant meta-analyses[37] and the unpublished European data on the LNG-20 IUS provided by Leiras (I Rauramo, Leiras Ltd: personal communication, 1999) found that that discontinuation because of menstrual changes varies widely across geographical locations (see pages 28 and 51). Therefore, results need to be interpreted at both an individual and community level. It is important to be aware that factors other than acceptability may affect continuation. In countries with very proactive population control policies, women may be pressured to continue with a method deemed by providers to be effective. Financial factors are likely to affect both initial choice of method and continuation. In the UK, for the most part, contraception is free and a woman's choice of method is not limited by personal expense, although access to certain methods may be limited because of high initial costs. In other countries, such as the USA, financial factors affecting the user are likely to have some influence.

Counselling

It is presumed that pre-treatment counselling, to ensure that women are informed about the potential side-effects of a contraceptive method, has a positive effect on continuation rates, but we could find little unbiased published evidence to support this assumption. We had intended to explore the effect of counselling on continuation rates and reasons for discontinuation, acknowledging that we would not be able to measure content or quality of the counselling, but were unable to do so.

A study in China[130] did find that women having DMPA injections who were counselled were less likely to discontinue because of menstrual disturbance than were those women who did not receive counselling. It is possible that women who receive adequate pre-treatment counselling about menstrual disturbance may be dissuaded from starting these methods in the first place. Women who decide to use the LNG-20 IUS may be more likely to continue if they are aware that they may experience amenorrhoea and that it has no adverse effects on their health. None of the studies provided information on the characteristics of women who refused enrolment, or reported whether counselling had dissuaded a women from her initial choice of contraceptive. It has been suggested that pre-treatment counselling is insufficient and that counselling needs to be continued during follow-up visits.[131]

Tolerability

Hormonal side-effects and menstrual disturbance

Very few data could be extracted on hormonal side-effects and menstrual disturbance. Amenorrhoea was the one outcome that both users of subdermal implants and IUSs were significantly more likely to experience.

The fact that so few data were available was not necessarily because authors had not reported these outcomes, but was due to the ways these outcomes had been measured. For instance, some investigators used the percentage of women experiencing an 'increase', 'decrease' or 'the same' as measurements for events such as dysmenorrhoea or headaches. This information is not useful as it does not inform the reader about the baseline rate, and how women themselves define symptoms will vary greatly depending on factors, such as parity and age, which need to be controlled for in the analysis. In the case of menstrual disturbance, recruitment should be restricted to women who have a regular and symptom-free menstrual cycle so that a more accurate measurement can be made of the effect a contraceptive method has on menstruation. In addition, the recommendation made by Rodriguez[24] that menstrual disturbance should be measured at 90-day intervals should be adhered to. Measurements of both rate of menstrual disturbance and rate of hormonal side-effects at time points such as a year are meaningless as they do not show when women started experiencing these outcomes or how long they experienced them. Discontinuation due to menstrual disturbance *per se* is not an informative outcome as the comparison of the LNG-20 IUS with IUDs > 250 mm^3 illustrates. Women using LNG-20 IUSs discontinued because of amenorrhoea, whereas IUD > 250 mm^3 users discontinued because of bleeding and pain. The reporting of discontinuation due to amenorrhoea, bleeding and pain must be collected separately to provide the true picture.

Local device problems

There was very little information on failed insertion or removal of implants and IUSs. It is possible that women who had problematic insertions were not enrolled onto the studies.

The evidence on the LNG-20 IUS suggested that women using this method were significantly more likely to expel the device than were IUD > 250 mm^3 users. To prevent local device problems, it has been

recommended that only healthcare workers who have received specialist training should insert and remove these implantable contraceptive devices.

Training

Insertion and removal of implants and IUSs are simple procedures, but do require specialist training. Blumenthal and colleagues conducted an RCT to investigate the different methods of implant insertion[132] and showed that the method used did have an impact on the speed and proficiency of the procedure. Ease of insertion and removal is likely to affect acceptability of contraceptive methods from the perspective of both the consumer and the practitioner. A study by Zimmerman and colleagues[133] found pain at insertion and removal of Norplant was of major concern to potential users. There has been adverse media coverage about problematic side-effects and difficult removals of Norplant experienced by a number of women. This led to a marked fall in the numbers of women requesting this method of contraception and to the manufacturer's withdrawal of Norplant in the UK.[134]

Although it was recognised that it would be impossible to measure the content or quality of training in the systematic reviews, it was hoped that it would be possible to explore the impact of training on rate of device problems through subgroup analysis. The fact that training was only mentioned in 9% of the subdermal implant studies and in none of the IUS studies prohibited further investigation.

Family planning practitioners who have not received appropriate training on insertion or removal are likely to favour alternative methods and may not offer subdermal implants or IUSs to women seeking contraceptive advice.

It was not possible to examine whether or not specialist service provision made any difference to outcomes (i.e. whether FPCs had better continuation rates than general practice settings).

Adverse events

Progestasert's licence was not renewed in the UK because of concerns about increased risk of ectopic pregnancy relative to copper-bearing IUDs. Too few studies were eligible for inclusion in the meta-analysis for this risk to be determined accurately (rate ratio, 3.0; 95% CI, 0.39 to 32.36).

It has been suggested that LNG-20 IUSs may decrease the incidence of PID in users, particularly in women younger than 25 years, by thickening the utero-cervical mucus.[42] Again, because of the paucity of data included in the meta-analysis, it was not possible to determine whether or not this was the case.

With regard to other adverse events for which data were collected, the rates for both implants and IUSs were very similar to the rates for the methods of contraception to which they were compared.

Other issues

Quality

The quality assessment of studies aims to reduce bias in the review either by excluding studies of poor quality altogether or by conducting sensitivity analysis on the high-quality studies to assess whether quality impacts on results. Studies of higher quality are less likely to be biased and are therefore more likely to measure the true 'treatment' effect. Although we recognise that authors are often restricted in their description of study methods by, for example, journal word-count limits, the poor initial inter-rater agreement on study quality reflected the lack of clarity by some study authors in describing the methods used and the characteristics of the investigated population.

It was decided to report quality of studies rather score quality (and then it was hoped to analyse the effects of the identified quality factors on the results through subgroup analysis). If double-blind trials, for example, were given greater weight in scoring systems, many studies of contraceptives would be discriminated against because of the impossibility of concealing the 'device/method'. However, allocation concealment is always feasible, even if unblinding happens immediately afterwards. Schulz and colleagues[135] demonstrated that inadequate or unclear allocation concealment, that is randomisation by clinic number or patient case number, exaggerated the treatment effect by 41% and 30%, respectively. Unfortunately, it was not possible to investigate what impact allocation concealment, as well as other quality factors, had on the findings because of the small numbers of eligible studies.

The fact that in most studies the investigators were not blind to the methods of contraception at follow-up visits for assessment of outcomes would not affect the number of pregnancies reported. However, reporting of hormonal side-

effects, PID and menstrual disturbance, and even continuation, could be affected by either the investigator or the contraceptive user knowing the method.

It was interesting to note that none of the studies in either of the reviews provided any information on the characteristics of those women who withdrew or were lost to follow-up. Loss to follow-up is a problem experienced in nearly all intervention studies. It is important to determine what effect loss to follow-up has had on the results. Firstly, is the loss to follow-up different between groups? The answer to this question may provide insight into the acceptability and tolerability of a contraceptive method because women who are dissatisfied with a method may be more likely to drop out of a study. Secondly, has loss to follow-up had any impact on the results? It may bias the results of a method's effectiveness. To account for this, one can assume the most favourable scenario (i.e. none of those lost to follow-up became pregnant), the least favourable scenario (i.e. all of those lost to follow-up became pregnant), or that the rate of pregnancy in those lost to follow-up is similar to the rate amongst those who have remained in the study.

Measurement

Although life tables have been recommended as the most appropriate way to analyse contraceptive efficacy data, and many of the included studies used this method, confusion arose because of inconsistency in the way these methods were defined and calculated. This resulted in the exclusion of some studies from the meta-analysis. It was much easier to extract data from papers on number of events and women months or women years to provide an estimate akin to the PI.

Synthesis of single decrement life-table probability differences is more likely to show the true effect than the synthesis of events per women months (see page 3). Life-table analysis did sometimes provide a significant difference in effect that was not evident when rate ratios were used. This highlights the need to be cautious when interpreting data from contraceptive effectiveness studies. For the purpose of synthesising contraceptive effectiveness data, single decrement life-table probabilities should be used whenever possible.

Publication bias

Exhaustive attempts were made to ensure that all relevant studies were located, but 'grey' literature and non-English language publications can be difficult to identify through search strategies. We were unable to determine whether publication bias had affected the findings, as for the most part the summary effect sizes for pregnancy outcomes were calculated from one or two studies. This source of bias has been well reported: studies that show positive findings are more likely to be submitted for publication and more likely to be accepted for publication.[9] Therefore studies of subdermal implant or IUS interventions in which no benefits were found relative to other contraceptive methods, or even studies in which negative effects were found, are less likely to be published. Attempts were made to remove this bias by contacting pharmaceutical companies and individuals conducting contraceptive research.

Cost-effectiveness

Incremental costs per pregnancy averted were calculated for subdermal implants and IUSs relative to a number of other contraceptive methods. For subdermal implants relative to other contraceptive methods, where a cost-effectiveness ratio is calculated, incremental costs per pregnancy averted range from £16,285 to £255,102. For IUSs relative to other contraceptive methods, where a cost-effectiveness ratio is calculated, incremental costs per pregnancy averted range from £721 to £17,739. These results focus on pregnancies averted as the outcome measure and not other factors that have an impact on choice and acceptability of methods (for example, differing baseline characteristics of users of different contraceptive methods). They are useful to healthcare decision makers who must decide upon appropriate provision of contraception given limited healthcare budgets. However, they must be treated with caution for a number of reasons.

Firstly, these cost-effectiveness analyses are useful for comparing contraceptive methods of similar default states. They are of more limited use for examining relative cost-effectiveness of methods for which user failure is an important determinant of effectiveness. The relative effectiveness of these methods was not examined in well-designed studies. The LNG-20 IUS was compared only with IUDs and Norplant-2. In most of the studies included in the meta-analysis, Norplant was compared with other implants and it was only compared with non-implantable methods in non-RCTs. In non-RCT studies, the differing baseline characteristics of participants make it difficult to interpret the results of relative effectiveness. It is likely that subdermal implants or IUSs would be

more cost-effective in pregnancy prevention if they were compared with more user-dependent methods, such as combined oral contraceptive pills, for which user failure and higher discontinuation rates are important factors. The analyses reported here have not been able to examine this because of restrictions arising from the limited amount of effectiveness data included in the meta-analyses. Secondly, it was possible to calculate only for up to 1 year the cost-effectiveness ratios for the subdermal implants or IUSs relative to the methods more reliant on user compliance.

Generally the cost-effectiveness ratios for subdermal implants and IUSs are quite high. This is explained by the low incremental effectiveness of subdermal implants and IUSs relative to other methods (i.e. all methods were effective in preventing unwanted pregnancy and therefore the differences found between methods were fairly small). Subdermal implants and IUSs are more costly at preventing pregnancies than the other methods included in the cost-effectiveness analysis and only slightly more effective. In terms of the calculation of the cost-effectiveness ratio this means that a small incremental cost is being divided by a very small number of pregnancies averted, resulting in a relatively large cost-effectiveness ratio. It would therefore appear that what is driving the results of the economic evaluation is the fact that the other contraceptive methods included in the economic evaluation are generally quite effective. Even though, on the limited evidence available, subdermal implants and IUSs are shown to be more effective than other contraceptive methods, the difference is only marginal.

In two instances, subdermal implants and IUSs are dominated by the contraceptive methods with which they were compared (Norplant versus DMPA for a duration of 1 year, and the LNG-20 IUS versus IUDs > 250 mm^3 for a duration of 1 year). In economic terms this provides an argument for using DMPA rather than Norplant and IUDs > 250 mm^3 rather than the LNG-20 IUS. Although the meta-analyses indicated that Norplant was as effective as DMPA injections, with no pregnancies in either group after 1 year follow-up, and that the LNG-20 IUS was effective as the IUD > 250 mm^3, with a rate ratio of 1.0 at 1 year, the net ingredient costs of Norplant and the LNG-20 IUS are greater. Therefore DMPA injections and IUDs > 250 mm^3 are less costly, in terms of preventing unplanned pregnancy, to the NHS.

The cost-effectiveness analysis does not take into account the acceptability and tolerability of the contraceptive methods. Both of these factors are likely to affect continuation. The costs saved through the non-contraceptive health benefits of subdermal implants and IUSs could be considered. (However, the aim of this analysis was to determine the cost-effectiveness of subdermal implants and IUSs relative to other reversible contraceptive methods in averting pregnancy.) For example, a trial in Finland found women with excessive menstrual bleeding using the LNG-20 IUS were less likely to have a hysterectomy than women in a control group who were using no contraceptive method.[11] Furthermore, the cost-effectiveness analysis does not account for the different risks of pregnancy in different populations because it was decided to use an NHS perspective for the general UK population.

Using the Trussell and Kost[15] pregnancy rate estimates in the sensitivity analyses instead of the rates estimated by the Steering Group had the effect of greatly reducing the incremental costs per pregnancy averted (*Table 40*). The incremental cost per pregnancy averted of Norplant relative to the IUD < 250 mm^3 at 1 year, for example, fell from £255,102 to £8129. Norplant remained dominated by DMPA injections after 1 year of use because the pregnancy rate estimates of the Steering Group were the same as those of Trussell and Kost. The data Trussell and Kost used for their estimates are predominantly from studies conducted in the USA, in particular the National Survey of Family Growth. The reduction in the incremental cost per pregnancy with the sensitivity analysis using the pregnancy rates estimated by Trussell and Kost may be explained by the definition of use – Trussell and Kost's failure rates are based on 'typical use'. The authors also provide 'lowest expected rates' and 'lowest reported rates', the first of these being "our best guess of a set of rates that would be expected among perfect users of methods". The pregnancy rates estimated by the Steering Group do fall within the range of Trussell and Kost's 'typical' estimates and the 'lowest reported' and 'lowest expected' estimates. Further sensitivity analysis could be conducted by varying the pregnancy estimates for the methods of contraception used for comparison. For example, poor compliance of contraceptive pill use in adolescents has lead to much higher rates of pregnancy in this group than indicated by the failure rates included in the cost-effectiveness analysis. Therefore subdermal implants would be more cost-effective if they were

compared with the contraceptive pill in this population group.

The results obtained in this economic evaluation are substantially different from those obtained in previous UK-based analyses. For example, McGuire and Hughes[1] estimate a cost per pregnancy avoided of FPC provision of various contraceptive methods ranging from £55 to £157 (reference 1, page 20). McGuire and Hughes used estimates provided by Trussell and Kost. One explanation for this difference in cost-effectiveness is that McGuire and Hughes calculate the cost-effectiveness of different methods of contraception relative to 'no method'. This gives the extra cost of preventing one pregnancy by introducing a new contraceptive method where none was used before. In the current evaluation, the alternatives compared were informed by the results of the systematic review and meta-analysis, and 'no method' was not included as a baseline scenario: cost-effectiveness was measured in all cases for subdermal implants and IUSs relative to some other method. In other words, the baseline alternative is different. Essentially, then, the economic evaluation presented here measures the cost-effectiveness of changing from one contraceptive method to another rather than of changing from using no method to using one specific method.

This economic evaluation was informed by the results of the systematic review and meta-analyses, which provided data on the alternatives to be compared, the duration of use of the alternatives compared, and the effectiveness of the alternatives (i.e. the relative risk of pregnancy across different contraceptive methods). Hence, only a limited number of comparisons were possible between subdermal implants and IUSs and other contraceptive methods. Clearly this diminishes the scope of the evaluation, though it would be inappropriate to make comparisons where no reliable data are available on relative effectiveness.

Clearly, a major shortcoming in the economic evaluation of subdermal implants and IUSs is the lack of good empirical data. What are needed are well-designed, large-scale, head-to-head trials that have adequate power to detect not only significant differences in effect, but also significant differences in side-effects, both of which are likely to have an impact on cost-effectiveness. Additionally, effort should be made to collect economic data on resource use, both for continuers and discontinuers of contraceptive methods, since both groups are likely to incur costs to the healthcare services. Only on this basis can appropriate recommendations be made concerning costs and cost-effectiveness.

Chapter 9

Conclusions and recommendations

Conclusions

Due to the paucity of evidence, these systematic reviews were unable to determine whether subdermal implants and IUSs were any more or less effective in preventing unwanted pregnancy than other reversible methods with which they were compared. However, women using either of these methods were more likely to experience amenorrhoea and this event was a notable reason for discontinuation.

A woman considering using either a subdermal implants or an IUS is going to want to know 'Which is the best method of preventing pregnancy for me?'. To date, family planning practitioners have had to rely on individual studies or use generic terms based on experience to answer this question. Therefore, the information that those seeking contraception receive is often biased and definitions of what is meant by 'effective' may vary.[13] Unfortunately, the comparative intervention studies that were identified were often unable to provide information to answer user-related questions.

Although these systematic reviews were unable to provide a definitive answer on the effectiveness of either subdermal implants or IUSs relative to other reversible contraceptive methods, they have raised issues concerning the conduct of contraceptive research. These included study quality, the interpretation of results and the difficulties in trying to synthesise contraceptive effectiveness data. Comparative intervention studies may not be the best way to inform practitioners and users about contraceptive effectiveness because women who agree to participate in RCTs are not going to be representative of the general population and because of the selection bias introduced into non-RCT prospective cohort comparisons.

Although Norplant has been withdrawn from the UK market, Implanon was launched in the autumn of 1999. Subdermal implants will continue to be a contraceptive option for women. Therefore, research into the effectiveness, tolerability, acceptability and cost-effectiveness of these methods needs to continue.

Recommendations

1. Standardisation of methods and measurements used in contraceptive research

These systematic reviews highlight the problems that arise because of inconsistent methods used to measure and report contraceptive effectiveness. Although we were not able to assess what impact these factors had on pooled data as we had initially hoped, standardised methods need to be encouraged, from the recruitment to analysis stages. These problems do not just impact on individuals conducting systematic reviews. They affect how healthcare practitioners, policy makers, contraceptive users, researchers and the media interpret the contraceptive literature, whether it comes from articles in peer-reviewed journals or from information leaflets on contraception.

Guidance has been provided by Trussel[14] on the methodological issues that need to be considered when undertaking as well as interpreting contraceptive efficacy and effectiveness research. Ways of measuring other outcomes, such as menstrual disturbance, have also been outlined.[22] We would advocate that these recommendations are considered when any contraceptive research that aims to measure effectiveness outcomes is being undertaken.

2. Consumer involvement in the development of contraceptive research

It is vital that contraceptive effectiveness research is able to answer the queries and concerns of contraceptive users. Unfortunately, this has not been the case to date. Although rates of unwanted pregnancy and continuation with the contraceptive method, and reasons for discontinuation of method, do provide information on acceptability and tolerability as well as on effectiveness, frequently there were few data on hormonal side-effects and menstrual disturbance. There is an assumption that women will discontinue methods if side-effects are problematic, which may or may not be the case. Women's choice and acceptance of different methods is likely to be affected by acceptability, tolerability and availability of alternatives and the

desire not to conceive. If contraceptive users are involved in research development, attention can be directed to answering consumer-related questions.

3. Randomised studies to assess the impact of counselling on discontinuation of subdermal implants and IUSs

Providing lengthy and detailed counselling has economic implications. These reviews were unable to determine what impact counselling had on continuation and user satisfaction. There is a general assumption that counselling works, and as many women discontinue use of these implantable contraceptives because of menstrual disturbance, it is clearly important that they understand that menstrual changes (in particular amenorrhoea for IUSs) are a possibility. An RCT is required to compare current practice with a programme giving counselling before the method is started and then ongoing counselling while the method is in use.

4. Well-designed prospective cohort studies to follow-up women using different contraceptive methods

The non-RCT prospective comparative cohorts allow comparison of a broader spectrum of contraceptive methods than do RCTs. However, the non-RCT studies included in these reviews were of poor quality. Although prospective cohort studies are not suitable for assessing the relative effectiveness of contraceptive methods, if well designed studies of this type can provide information on outcomes such as insertion and removal difficulties with subdermal implants.

5. Evaluation of training

An evaluation of training for healthcare professionals in the insertion and removal of implantable contraceptives is required to determine what is most effective.

6. Inclusion of economic endpoints in primary research

In the pursuit of great rigour in methods for conducting economic evaluations, clearly what are needed are well-designed, large-scale, head-to-head trials that have adequate power to detect not only significant differences in effect, but also significant differences in side-effects, both of which are likely to have an impact on cost-effectiveness. Moreover, in a world in which cost and budget constraints are becoming increasingly important, these trials should collect economic data on resource use, so that appropriate recommendations can be made concerning costs and cost-effectiveness, as well as clinical effectiveness.

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Appendix 1

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Appendix 2

Pre-defined secondary outcomes

Pregnancy rate after implant removal at 1 and 2 years
Rate of failed implant removal

Rate of hormonal side-effects:
- headaches
- pelvic pain
- breast tenderness
- acne
- weight gain
- nausea/vomiting
- dizziness/vertigo
- hair growth
- hair loss
- ovarian cysts
- uterine cramps
- mood changes

Rate of menstrual disturbance:
- dysmenorrhoea
- spotting
- oligomenorrhoea
- amenorrhoea
- menorrhagia
- prolonged bleeding

Rate of local device problems:
- local sepsis
- malposition
- translocation
- expulsion

Rate of adverse clinical events:
- ectopic pregnancy
- PID
- anaemia
- breast cancer
- fibroids
- vaginitis
- urinary tract infection
- cervical intraepithelial neoplasia I
- cervical intraepithelial neoplasia II
- cervical intraepithelial neoplasia III
- invasive cervical cancer
- myocardial infarction
- stroke
- pulmonary embolism/thrombophlebitis
- gall bladder disease
- death

Reason for discontinuation:
- hormonal side-effects
- menstrual disturbance
- adverse clinical event
- local device problem
- planning pregnancy
- patient choice – other

Appendix 3

Search strategy

The search strategy illustrated below was used to identify relevant studies on MEDLINE. Thesaurus terms and truncation symbols were adapted for the other databases as required.

1. "INTRAUTERINE-DEVICES,-MEDICATED"/all subheadings
2. INTRAUTERINE SYSTEM* OR IUS
3. CONTRACEPTI* near IMPLANT*
4. Explode "NORGESTREL"/all subheadings
5. "LEVONORGESTREL"/all subheadings
6. NORGESTREL
7. LEVONORGESTREL
8. ETONORGESTREL
9. KETO near DESOGESTREL
10. NORPLANT*
11. UNIPLANT
12. IMPLANON
13. PROGESTASERT
14. MIRENA
15. LEVONOVA
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Appendix 4

Data collection form*

Primary outcome measures	Units of measurement	Intervention =	Control =
Pregnancy due to method/user failure			
1 year	Life table prob. (SE) n women months		
2 years	Life table prob. (SE) n women months		
3 years	Life table prob. (SE) n women months		
4 years	Life table prob. (SE) n women months		
5 years	Life table prob. (SE) n women months		
Continuation			
1 year	Life table prob. (SE) n women months		
2 years	Life table prob. (SE) n women months		
3 years	Life table prob. (SE) n women months		
4 years	Life table prob. (SE) n women months		
5 years	Life table prob. (SE) n women months		

* The same format was used to collect secondary outcome measures for intervention and control groups, with the exception of menstrual disturbance, hormonal side-effect, failed removal and planned pregnancy outcomes for which number of events and number of women at follow-up were collected, and weight gain, for which mean weight gain with SDs were collected.

Appendix 5

Characteristics of excluded studies

TABLE 42 *Excluded subdermal implant studies*

Study	Intervention	Primary outcomes	Reason for exclusion
Huber, 1999[40]	Implanon vs. Norplant	Serum etonorgestrel concentrations	Reported outcomes not relevant to review (other publications of studies were included – see Implanon studies[37])
Fleming, *et al.*, 1998[136]	Norplant vs. IUD	Continuation	Retrospective cohort
Singh & Ratnam, 1997b[137]	Norplant vs. Cu IUD	Lipid, lipoprotein and apolipoprotein metabolism	Reported outcomes not relevant to review
Singh, *et al.*, 1997b[138]	Norethidrone acetate implant vs. Cu IUD	User satisfaction	Retrospective survey
Bromham, 1995[139]	Norplant vs. oral contraceptives	Insertion problems	Only report Norplant outcomes
Datey, *et al.*, 1995[140]	Subdermal implants, injectables, IUDs and oral contraceptives	N/A	Review article
Diaz, *et al.*, 1995[141]	Nestorone™ implants vs. Cu IUD	Pregnancy, reasons for discontinuation, ovarian function, and serum progesterone, oestradiol and Nestorone levels	Data on outcomes relevant to review not reported for IUD controls
Ding, *et al.*, 1995[142]	Norplant, Implanon and Sino Implant	Effect on lipid metabolism and immunoglobulin	Reported outcomes not relevant to review
Dinerman, *et al.*, 1995[143]	LNG implants, oral contraceptives, condoms and nothing (all groups encouraged to use condoms)	Pregnancy, continuation, sexually transmitted diseases, hormonal side-effects, sexual activity and user satisfaction	Non-intervention study – 6-month survey
Noerpramana, 1995[144]	Norplant vs. IUD	Pregnancy, continuation, reasons for discontinuation, menstrual disturbance and hormonal side-effects	Retrospective cohort
Blumenthal, *et al.*, 1994[145]	Norplant, condoms, oral contraceptives and nothing	Pregnancy, continuation, reasons for discontinuation and user satisfaction	Retrospective follow-up study
Gu, *et al.*, 1994[146] Du, *et al.*, 1990[147] Gu, *et al.*, 1989[148] Gu, *et al.*, 1988[149]	Norplant vs. Norplant-2	Pregnancy, continuation, reasons for discontinuation, menstrual disturbance and hormonal side-effects	Comparison of two separate cohorts
Mascarenhas, *et al.*, 1994[150]	Norplant vs. Implanon	Continuation, reasons for discontinuation and user satisfaction	Results for methods not reported separately
Shen, *et al.*, 1994[151]	Norplant, oral contraceptive pill and stainless steel ring IUD	Blood pressure changes	Reported outcomes not relevant to review
Qifang, *et al.*, 1994[152]	Norplant, oral contraceptives and stainless steel IUD	Blood pressure changes	Reported outcomes not relevant to review

N/A, not applicable

continued

TABLE 42 contd *Excluded subdermal implant studies*

Study	Intervention	Primary outcomes	Reason for exclusion
London, 1993[153]	LNG implants vs. DMPA injections	N/A	Review
Xiao, *et al.*, 1993[154]	Norplant vs. LNG-IUS	N/A	Review article
Shaaban, 1991[155]	Norplant, injectable (NET-EN) and IUDs	Effect on breastfeeding and infant growth and development	Reported outcomes not relevant to review
Diaz, *et al.*, 1991[156]	Various doses of 3-keto desogestrel implants compared	Ovarian function and menstrual disturbance	Some women using other forms of contraception
Darney, *et al.*, 1990[157]	Norplant vs. Norplant-2	Method acceptability and user satisfaction	Non-intervention study
Singh, *et al.*, 1990[158]	Norplant vs. Norplant-2	Liver function, and lipid and carbohydrate metabolism	Reported outcomes not relevant to review
Koifman, *et al.*, 1987[159]	Norplant vs. oral contraceptives	Hormonal and menstrual side-effects	Cross sectional study
Affandi, *et al.*, 1986[160]	Norplant vs. Cu IUD	Effect on lactation and infant growth	6-month follow-up reported
Toppozada, *et al.*, 1986[161]	Norplant, Cu IUD and oral contraceptives	Vaginal candidiasis	Reported outcomes not relevant to review
Robertson, *et al.*, 1985[162]	Norplant 4 rods vs. 6 rods	Pregnancy, continuation, reasons for discontinuation and menstrual disturbance	Comparison of two separate cohorts
Sivin, *et al.*, 1983[163]	Norplant and Norgestrienone (R2010) implants vs. CuT 200 IUD	Pregnancy, continuation, menstrual disturbance and reasons for discontinuation	IUD group recruited over different time period
Sivin, *et al.*, 1980[84]	Norplant vs. Norgestrienone (R2010) implants	Pregnancy, continuation, reasons for discontinuation, insertion and removal problems, and user satisfaction	Combines results of RCT of Norplant and Norgestrienone implants (see Nielson, *et al.*, 1979[57]) with non-comparative Norplant study
Croxatto, *et al.*, 1982[164]	Progesterone implants, CuT 200 IUD and injectable placebo	Pregnancy, reasons for discontinuation, effect on lactation and infant growth	Majority of implant group are on additional contraceptive methods

N/A, not applicable

TABLE 43 *Excluded IUS studies*

Study	Intervention	Primary outcomes	Reason for exclusion
Diaz, *et al*., 1993[126]	LNG-IUS vs. CuT 380Ag IUD	Pregnancy, continuation and reasons for discontinuation	Only report LNG-IUS outcomes. Comparative results reported elsewhere. (See Sivin & Stern, 1994[73])
Faundes, *et al*., 1993[127]	LNG-IUS vs. CuT 380Ag IUD	Pregnancy, continuation, reasons for discontinuation, ovarian function and LNG serum levels	Only report LNG-IUS outcomes. Comparative results reported elsewhere. (See Sivin & Stern, 1994[73])
Xiao, *et al*., 1993[154]	LNG-IUS vs. Norplant	N/A	Review article
Yin, *et al*., 1993[165]	LNG-IUS, stainless steel ring, and CuT 220 IUD	Endometrial mast cell density	Reported outcomes not relevant to review
Pedron Neueo, 1992[166]	11 IUSs and IUDs of various types	Menstrual blood loss	Reported outcomes not relevant to review
Penghi, *et al*., 1991[167] Zhu, *et al*., 1989[168]	LNG-IUS, stainless steel ring and CuT 220 IUD	Bleeding profile and endometrial activity	Reported outcomes not relevant to review
Gupta, *et al*., 1989[169]	Women having discontinued CuT 200, CuT 220, Cu 7, CuT 380, Multiload 250, Nova-T, IPCS 52 or Lippes Loop in order to become pregnant (cohort from five prospective cohorts of comparisons of the above methods)	–	Unable to extract data on individual methods
Faundes, *et al*., 1988[170]	LNG-IUS, CuT 380AG IUD, Lippes Loop IUD and non-IUD users	Haemacrit and blood ferratin levels	Reported outcomes not relevant to review
Jovanovic, *et al*., 1988[171]	Progestasert vs. non-IUD users (combination of oral contraceptives, barrier methods, rhythm method and nothing)	PID	Unable to extract data
Ulstein, *et al*., 1987[172]	LNG-IUS vs. Cu IUD	Changes in cervical and vaginal microflora	Reported outcomes not relevant to review
Nilsson, *et al*., 1986[128] (Other publications are included in the review[101])	LNG (20 µg/day) vs. LNG (30 µg/day) IUSs	Plasma concentration of LNG	Reported outcomes not relevant to review
Calzolari, *et al*., 1985[173]	Progestasert IUS vs. Cu IUD	Pregnancy, user satisfaction	Retrospective study. Women perimenapausal
Pedron, *et al*., 1981[174]	LNG-IUSs (2 µg/day and 4 µg/day), Norgestrel IUS (10 µg/day) and Progestasert (40 µg/day and 65 µg/day)	Menstrual blood loss	Reported outcomes not relevant to review
Gibor & Phariss, 1980[175]	Various IUSs and IUDs	N/A	Review article
Hary, *et al*., 1979[176]	Progestasert (65 µg/day) vs. CuT IUD	Ovarian function	Reported outcomes not relevant to review
Pharriss, 1978[177]	Progestasert vs. other IUDs	N/A	Review article
Hefnawi, *et al*., 1977[178]	Lippes Loop D IUD (inert, AMCA-releasing and Cu clad), U-IUD (inert and progesterone-releasing) and CuT200 IUD	Menstrual blood loss	Reported outcomes not relevant to review
Nilsson, *et al*., 1977[179]	d-Ng-releasing IUS (25 µg/day) vs. Nova-T 200 IUD	Menstrual blood loss	Reported outcomes not relevant to review
Gyozo, 1976[180]	Progesterone-releasing IUS (65 µg/day) vs. inert IUD	Pregnancy and reasons for discontinuation	Control group not relevant to review – described by authors as a 'placebo'
Manuilova, *et al*., 1975[181]	Cu Lippes Loop IUD vs. polyethylene Lippes Loop IUD		Intervention not relevant to review

Appendix 6

Quality assessment of included studies

TABLE 44 *Subdermal implant studies quality assessment: RCTs*

	Implanon trials[37–42]	**Sivin, *et al.***[45,46]	**Wang, *et al.***[47–49]	**Darney, *et al.***[50,51]	**Olsson, *et al.***[52–54]	**Pasquale, *et al.***[55]	**Hingorani, *et al.***[56]	**Nielsen, *et al.***[57–60]	**Alvarez, *et al.***[61]
Study design Method of randomisation	Not stated	Blocks of 50; sealed envelopes	Sequential identification number; sealed envelopes	Not stated	Linear congruent method; sealed envelopes	Not stated	Not stated	Not stated	Not stated
Participant selection Description of previous contraceptive method		✔	✔	✔	✔	✔		✔	✔
Blinding Allocation concealment		✔	✔		✔	✔		✔	
Blinded assessment of outcomes								✔	
Measurement Groups treated identically	✔	✔	✔		✔	✔	✔	✔	
Follow-up Description of withdrawals and lost to follow-up									
Analysis Method of analysis for pregnancy/ discontinuation	PI	LT (single)	LT (single)	Other	LT (single) LT (multiple) PI	Other	LT (single)	LT (single) LT (multiple)	LT
User/method failure reported	N/A	N/A	✔	✔	✔	✔	N/A	✔	
Active follow-up		✔						✔	

LT, life table

TABLE 45 *Subdermal implant studies quality assessment: non-RCTs*

	Del Carmen Cravioto, *et al.*[44]*	Diaz, *et al.*[62]	Noerpramana[63]	Singh & Ratnam[64]	Abdel Aleem, *et al.*[65]	Hollander[66,67]	Mainwaring, *et al.*[68]	Cromer, *et al.*[69]	Fakeye[70,71]	Sivin, *et al.*[72]
Participant selection										
Groups similar at entry (see 'Study characteristics' for further details)	✔						✔			
Description of previous contraceptive method	✔	✔	✔	✔	✔	✔				✔
Blinding										
Blinded assessment of outcomes					✔					
Measurement										
Groups treated identically		✔	✔	✔	✔	✔		✔	✔	✔
Follow-up										
Similar follow-up in groups	✔		✔	✔	✔	✔	✔	✔	Variable	✔
Description of withdrawals and lost to follow-up										
Control for confounding										
In study design					✔	✔		✔		
In study analysis						✔				
Analysis										
Method of analysis for pregnancy/ discontinuation	LT	Other	Other	LT	LT	LT	N/A	Other	Other	LT
User/method failure reported	✔		N/A	✔	N/A	✔	N/A	N/A	N/A	N/A
Active follow-up							N/A			

**RCT – but included in prospective cohort category because one of the arms of the trial was suspended for 4 months*

continued

TABLE 45 contd *Subdermal implant studies quality assessment: non-RCTs*

	Singh, *et al.*[74]	**Affandi, *et al.*[75]**	**Diaz, *et al.*[76]**	**Lopez, *et al.*[77]**	**Roy, *et al.*[78]**	**Shaaban, *et al.*[79,80]**	**Kurunmaki[81]**	**Marangoni, *et al.*[82]**	**Croxatto, *et al.*[83]**
Participant selection									
Groups similar at entry	✔	✔					✔		
Description of previous contraceptive method		✔	✔	✔	✔		✔		
Blinding									
Blinded assessment of outcomes									
Measurement									
Groups treated identically			✔		✔	✔	✔	✔	
Follow-up									
Similar follow-up in groups	✔		✔		✔	✔		✔	
Description of withdrawals and lost to follow-up	✔				N/A				
Control for confounding									
In study design		✔			✔		✔		
In study analysis									
Analysis									
Method of analysis for pregnancy/ discontinuation	LT		LT (single)	LT (single) LT (multiple)	Other	LT	Other	LT	PI
User/method failure reported	✔	N/A	N/A			✔	N/A		✔
Active follow-up									

TABLE 46 *IUS studies quality assessment*[*]*: RCTs*

	Pakarinen, *et al.*[87]	**Andersson, *et al.*[43,88–92]**	**Sivin, *et al.*[73,93–97]**	**Wang, *et al.*[47–49]**	**Baveja, *et al.*[98]**	**Andrade, *et al.*[85†]**	**WHO[99]**	**Lavin, *et al.*[100]**
Study design Method of randomisation	Opaque sealed envelopes	Envelopes	Blocks of 50; opaque envelopes	Sequential identification number; sealed envelopes	Computed; sealed envelopes	Random numbers table	Computed tables; sealed envelopes	Not stated
Participant selection Description of previous contraceptive method		✔		✔		✔		✔
Blinding Allocation concealment	✔	✔	✔	✔	✔		✔	✔
Blinded assessment of outcomes		‡						
Measurement Groups treated identically	✔	✔	✔	✔	✔		✔	
Follow-up Description of withdrawals and lost to follow-up								✔
Analysis Method of analysis for pregnancy/ discontinuation	LT (single)	LT (single) LT (multiple)	LT(single) LT (multiple)	LT (single)	LT (single)	N/A	LT (single)	Other
User/method failure reported	✔	✔	✔ ✔	✔	✔	N/A	✔ ✔	

[*] *The WHO 1997 trial*[86] *was excluded from the quality assessment as it is still in progress and information about the study was obtained from a summary update. The Affandi and colleagues study*[112] *was excluded because information about the study was obtained from an abstract*
[†] *RCT cohort only*
[‡] *Women blinded to method*

continued

TABLE 46 contd *IUS studies quality assessment*: RCTs*

	Nilsson, *et al.*[101–104]	**Rybo & Bergqvist[105]**	**WHO[106,107]**	**el Mahgoub[108,109]**	**Heikkila[110]**	**Larsen, *et al.*[111]**	**Newton, *et al.*[113]**	**Pizarro, *et al.*[114,115]**	**Fylling & Fagerhol[116]**
Study design									
Method of randomisation	Tables	Not stated	Computed; sealed envelopes	Not stated	Not stated	Not stated	Not stated	Computed tables	Not stated
Participant selection									
Description of previous contraceptive method				✔	✔			✔	
Blinding									
Allocation concealment	✔		✔			*	✔		
Blinded assessment of outcomes							✔	✔	
Measurement									
Groups treated identically	✔	✔	✔			✔	✔	✔	✔
Follow-up									
Description of withdrawals and lost to follow-up									
Analysis									
Method for analysis of pregnancy/ discontinuation	LT (single) Other LT (multiple) PI		LT (single)	LT	Other	LT (multiple)	LT	LT	Other
User/method failure reported	✔		✔		N/A			✔	
Active follow-up			✔						

* *Women blinded to method*

TABLE 47 *IUS studies quality assessment: non-RCTs*

	Sivin, *et al.*[72]	**Diaz, *et al.*[117]**	**Heikkila, *et al.*[118]**	**Reynoso, *et al.*[119]**	**Diaz, *et al.*[120]**	**Feichtinger, *et al.*[121]**	**Pizarro Orchard, *et al.*[122]**	**Gozzi & Quadrani[123]**	**Nilsson[124]**	**Martiez Manautou, *et al.*[125]**
Participant selection										
Groups similar at entry		✔				✔	✔			
Description of previous contraceptive method	✔	✔	✔	✔		✔	✔	✔		
Blinding										
Blinded assessment of outcomes										
Measurement										
Groups treated identically	✔				✔	✔	✔			✔
Follow-up										
Similar follow-up in groups	✔	✔		✔	✔		✔		✔	✔
Description of withdrawals and lost to follow-up										
Control for confounding										
In study design			✔							
In study analysis										
Analysis										
Method for analysis of pregnancy/ discontinuation	LT	LT	Other	LT	PI	LT	LT	Other	N/A	LT
User/method failure reported	N/A		✔						N/A	
Active follow-up									N/A	

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We look forward to hearing from you.

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