Guest Editor:
Regine Sitruk-Ware

In this issue:
The levonorgestrel-releasing intrauterine system, Mirena®
Contraceptive efficacy and safety
Use in nulliparous women
Alternative to tubal occlusion
Menorrhagia
Leiomyoma-related bleeding
QOL and cost-effectiveness vs. hysterectomy
Endometriosis and dysmenorrhoea
Peri- and postmenopause
Endometrial effects
Future options

Medical Forum International
Contents

Editorial ................................................................. 2
Overview article
The levonorgestrel-releasing intrauterine system (Mirena®)
Regine Sitruk-Ware .................................................. 3
Review articles
Contraceptive efficacy and safety of the levonorgestrel-releasing intrauterine system (Mirena®)
Tapani Luukkainen, Päivi Pakarinen .......................... 4
Can the levonorgestrel-releasing intrauterine system (Mirena®) be used in nulliparous women?
Sarah Prager, Philip Darney ...................................... 7
The levonorgestrel-releasing intrauterine system (Mirena®) as an alternative to tubal occlusion
Ian Milsom .......................................................... 10
The levonorgestrel-releasing intrauterine system (Mirena®) in the treatment of menorrhagia
Bilian Xiao .......................................................... 13
The levonorgestrel-releasing intrauterine system (Mirena®) in the treatment of leiomyoma-related bleeding
Vera Halpern, Marina Tarasova .................................. 15
Quality of life and cost-effectiveness of the levo-
norgestrel-releasing intrauterine system (Mirena®) and hysterectomy in menorrhagia
Ritva Hurskainen .................................................. 19
The levonorgestrel-releasing intrauterine system (Mirena®) in endometriosis and dysmenorrhoea
Luis Bahamondes, Carlos A. Pelta ............................. 22
The levonorgestrel-releasing intrauterine system (Mirena®) in the peri- and postmenopause
David Sturdee ...................................................... 25
Endometrial effects of levonorgestrel intrauterine delivery
Takeshi Maruo ..................................................... 27
Future options for the intrauterine delivery of progestogens in the prevention of gynaecological disease
Ian S. Fraser .......................................................... 30

Subscription rate (Volume 11, 2006, 4 issues): individual – € 150/year; institutional – € 175/year (including postage and handling). Subscriptions are accepted with prepayment only. Orders should be addressed to: Medical Forum International, Attn Subscription Dept, PO Box 655, 3700 AR Zeist, The Netherlands, fax: +31 30 6930162.

Although great care has been taken to ensure accuracy, Medical Forum International shall not be liable for any errors or inaccuracies in this publication. Opinions expressed are those of the authors. The publishers and editors shall not be liable for the validity of clinical treatments, dosage regimens or other medical statements made. All dosages referred to should be checked against the relevant product data sheets.
Dear Colleagues

Most new medical drugs or developments suffer a pendulum effect with regard to their popularity and use. They are introduced with a fanfare and used widely and enthusiastically, only to find that after a year or two of general use side effects and difficulties emerge which had not been predicted or expected from the phase III studies. Confidence in the method wanes and its use decreases dramatically. There then often follows a realization that the method is useful for a particular population of patients or in certain circumstances and its popularity rises again.

The introduction of Mirena® has not followed this course; in fact, quite the reverse. Any initial concerns about pelvic inflammatory disease or the use of Mirena® in nulliparous women have been dispelled and new indications for its use in conditions such as menorrhagia, postmenopausal hormone replacement therapy, endometriosis, or for contraception in renal disease or after malignancy have emerged. Over 60 million couples currently use female sterilization as their method of contraception. Surely this number needs to be reduced by a cheaper, safer, more efficacious and reversible method.

Dr Sitruk-Ware and her team have expertly put together this edition of Gynaecology Forum, which is the third we have produced on the topic of Mirena® in the last 10 years. Each new issue illustrates the widening usefulness of the system. We need to use it more often.

Stephen Killick
Editor-in-Chief
Intrauterine contraceptive devices (IUDs) have been widely used since 1960. This method of contraception is extremely effective, with an effectiveness rate that is similar to that of tubal interruption (female sterilization), yet it is rapidly reversible. The types of IUDs have evolved from the original plastic (inert) devices to the current devices that release copper or levonorgestrel (termed intrauterine systems). Unwarranted concerns about IUDs limited their use in the United States to less than 1% of female contraceptive users compared with 30% in Europe and China.

The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) was developed as a long-acting method of contraception. The concept was invented by Tapani Luukkainen and developed by the Population Council in the late 1980s and early 1990s with the objective of improving the contraceptive efficacy and decreasing the bleeding days of the inert IUDs. The development was then completed in collaboration with the pharmaceutical companies Leiras in Finland and then Schering, and the system was first introduced in Finland in 1990. This medicated device inserted into the uterus is one of the most effective methods of contraception and is presently approved in over 100 countries for 5 years of use, including in the United States where the system was approved in 2000.

The LNG-IUS releases daily small amounts of levonorgestrel, a synthetic progestogen derivative, into the uterine cavity during a long wearing period. The system consists of a T-shaped plastic frame, to the vertical arm of which a cylinder containing the active substance mixed with polydimethyl siloxane (PDMS) is attached. The total amount of levonorgestrel in the cylinder is 52 mg. The cylinder is covered by a rate-controlling PDMS membrane that regulates the daily release rate of the hormone. Initially, the release rate is 20 μg/day, which declines to 11 μg/day at the end of 5 years. The mean release rate is 14 μg/day over the 5-year wearing period. The distal end of the T-frame contains two removal threads. The T-frame also contains barium sulfate, which makes it visible on x-ray examination.

The LNG-IUS directly targets the endometrium by releasing the potent progestogen levonorgestrel in low daily doses into the uterine cavity. The result is high local levonorgestrel concentrations that achieve uniform suppression of endometrial proliferation, inactive histology, thin epithelium and decidualization of the stroma. Such dramatic alteration of the endometrium creates an environment within the uterus that is unsuitable for sperm survival and fertilization and is thus a key mechanism of action for contraception. Although the circulating levels of levonorgestrel are very low, side effects related to the androgenic properties of levonorgestrel have been reported. In addition, insertion of the system needs a skilled health provider and may be difficult or painful when the uterus is small or atrophic. The development of smaller devices is warranted in these specific indications.

Besides its main indication for contraception, the advantages of direct action of levonorgestrel on the endometrium have been studied in other medical conditions. By inactivating the endometrium, the LNG-IUS is able to provide a range of other health benefits. These include treatment of idiopathic menorrhagia and associated anaemia or menorrhagia due to leiomyomata. The LNG-IUS also provides protection against endometrial proliferation in women receiving estrogen therapy.

The guest authors in this issue of *Gynaecology Forum* have reviewed the major aspects of the efficacy and safety of the LNG-IUS in several populations and provide recommendations about the appropriate indications and safe conditions for use of the system in young women as well as in postmenopausal women in countries where the product is licensed. Unfortunately the system is not yet widely available in developing countries where the dual benefits of a long-term contraceptive that reduces bleeding and hence prevents anaemia are of the utmost interest.

The size of the system that contains a reservoir delivering the progestogen may create difficulties for insertion in some women; thus, appropriate training of health care providers is required. New developments of a smaller system are ongoing and will offer an additional option to potential users.

**Suggested reading**


Contraceptive efficacy and safety of the levonorgestrel-releasing intrauterine system (Mirena®)

Tapani Luukkainen1 Päivi Pakarinen2

1Steroid Research Laboratory, Institute of Biomedicine, University of Helsinki, Helsinki, Finland
2Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland
(paivi.pakarinen@hus.fi)

Contraceptive efficacy

The mode of action of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) is to prevent fertilization not implantation [1]. The best experimental evidence for the mechanism of action was presented in a recent report by Munuce et al. [2]. The authors showed that concentrations of levonorgestrel above 400 ng/ml, which are similar to those found in the uterine cavity, can modify in vitro the expression of zona pellucida receptors on spermatozoa. This could also explain why the LNG-IUS is ineffective if inserted into the myometrium. The local release of levonorgestrel in the LNG-IUS produces concentrations of between 470 and 1500 ng/g wet tissue weight in the endometrium within weeks of insertion [3]. Circulating levels range from 150 to 200 nmol/l after the first few weeks.

The contraceptive effectiveness of the LNG-IUS does not depend on the age of the user (Table I). All other contraceptive methods including sterilization have high failure rates in young women. Our large randomized comparative trial in five European countries revealed not a single pregnancy during 5 years of use in women below 25 years of age in any of the participating countries [4]. The higher failure rate in all age groups using a copper-releasing intrauterine device (IUD) shows the superior effectiveness of the LNG-IUS.

Faundes et al. [5] reported no pregnancies during 7 years and 1018 woman-years of LNG-IUS use. Cumulative 7-year net rates revealed a low expulsion rate of 4.4 per 100 women and a low discontinuation rate due to bleeding of 1.8 per 100 women. This report is in agreement with other studies reporting a zero pregnancy rate with the LNG-IUS [1]. The report of Faundes et al. has an interesting conclusion for developing countries: ‘Preference for the copper IUD could be a sound public health policy, consistent with scarce resources. It does not take into account, however, the individual needs of women already debilitated by overt or subclinical anaemia, and the long-term cost-benefit ratio of saving versus increasing menstrual blood loss in these women.’

The hypothesized mechanism of action described by Munuce et al. [2] explains the absence of ectopic pregnancies when the LNG-IUS is correctly placed in the uterine cavity. A summary of the above studies covered 12,000 woman-years of LNG-IUS use without the occurrence of a single ectopic pregnancy. In women not using contraception, the expected number of ectopic pregnancies is between 7.5 and 10.6 per 1000 woman-years in those aged 25–34 years [6]; thus in 12,000 woman-years we would expect between 90 and 127 ectopic pregnancies, which illustrates the effectiveness of the LNG-IUS at preventing ectopic pregnancy.

The LNG-IUS has been shown to be effective in a range of situations. Abortion usually results from contraceptive failure or misuse. For example, a woman may have opted for a contraceptive method that was too difficult for her to use consistently or that had side effects leading to discontinuation. Eventually her choice of contraception failed to protect her from unwanted pregnancy. The decision to have an abortion is always a difficult one and afterwards requires an effective and usually long-term contraceptive method. The LNG-IUS can and should be inserted immediately after abortion, since the return of fertility is immediate [7]. The LNG-IUS is highly effective and does not need to be remembered every day. Other alternative reversible contraceptives have a higher

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Copper-releasing IUD (n = 937)</th>
<th>LNG-IUS (n = 1821)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤25</td>
<td>3.2</td>
<td>0</td>
</tr>
<tr>
<td>≥26–30</td>
<td>1.4</td>
<td>0.07</td>
</tr>
<tr>
<td>31–35</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>≥36</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>
failure rate and are less cost-effective in the long term [8]. Women at the time of abortion are highly motivated to consider contraception and, because of the surgical procedure, are already in a sterile environment in the operating theatre. Insertion of the LNG-IUS after evacuation of the uterine cavity is easy because the cervical canal is widened and the patient is under anaesthesia.

In developed countries a high percentage of women are overweight. The prevalence of obesity is increasing among young, fertile women. Their pregnancies have a high risk of complications. Young, obese women need a highly effective contraceptive method to prevent unplanned pregnancy. Because of the volume and increase in steroid solvent (fat in obese women), oral contraceptives are less effective and the risk of venous thromboembolism is increased [9]. Like oral contraceptives, steroid implants, contraceptive patches and vaginal rings are also less effective in obese women. In these women even a minor surgical procedure is problematic. Abortion is more difficult to carry out and even sterilization has obesity-dependent complications. The World Health Organization gives both the copper-releasing IUD and the LNG-IUS a category 1 rating for obese women, indicating that there are no safety concerns. The interested reader is referred to an excellent editorial in Contraception [10].

The LNG-IUS cannot be used for emergency contraception. If a woman has a cervical or endometrial infection, insertion should be postponed until the infection has been treated.

Safety

The LNG-IUS has been used by over 8,500,000 women (February 2006) and is marketed as a contraceptive in 107 countries (data from Schering Oy Finland, Information Centre). In the literature there are 1395 scientific reports of the LNG-IUS, none of which mention serious side effects or safety concerns. The LNG-IUS is a well-established contraceptive. However, there are adverse effects related to any contraceptive. During the first months after insertion of the LNG-IUS, the patient may experience transient hormonal side effects including oedema, headache, breast tenderness and acne or other skin problems [11]. Lower abdominal or back pain, vaginal discharge and nausea have also been reported [12]. Functional cysts are typical during the use of progestogen-only contraception, but they vanish spontaneously [13]. Spotting is quite common during the first few months, but by the end of the first year of use 20–35% of women are amenorrhoeic. The reason for the amenorrhoea is the suppression of the endometrium by locally released levonorgestrel. Ovarian function remains unchanged [14].

Before coming to the market, the LNG-IUS was studied in two randomized comparative 5-year trials [12, 15]. Several specific studies were carried out on the effects of use on metabolic events and local microscopic changes in the endometrium during long-term use [16, 17]. All the materials were thoroughly tested and found to be suitable for human use when placed in the uterine cavity. The results of all these studies resulted in approval by all European registration agencies as well as by the United States Food and Drug Administration (FDA).

Anaemia and iron stores

Compared with the copper-releasing IUD, the LNG-IUS decreases the duration of menstruation and blood loss, thus increasing body iron stores and treating anaemia [18].

Pelvic inflammatory disease

The decrease in the duration of menstruation and the associated blood loss, inactivation of the endometrium and possible changes in the cervical mucus help to prevent the progression of cervical infection to endometritis and pelvic inflammatory disease [12, 19]. The rate of infection in young women using the LNG-IUS was significantly lower in comparison with those using the copper-releasing IUD at 3 and 5 years of use. However, insertion-related infections were eliminated by maintaining asepsis during insertion of both devices. This is important to protect future fertility and requires only a minor effort by the attending medical personnel. The recovery of fertility after LNG-IUS removal is rapid and reaches normal values for planned pregnancy [20]. The LNG-IUS is a suitable replacement for irrevocable contraception, sterilization, in women of reproductive age.

Lactation

Insertion of the LNG-IUS should be performed between 6 and 8 weeks after delivery following these instructions: do not use the sound, release the arms low in the uterine cavity, wait for the arms to open and lift gently to the fundal part of the cavity, then release the device. The levonorgestrel released from the LNG-IUS in the mother’s circulation and in her breast milk is very low. Only 0.1% of the maternal daily dose is present in the milk [21–23]. This low amount of levonorgestrel does not harm the development or growth of the newborn [24, 25]. A positive effect of providing safe and effective contraception in breast-feeding mothers was the increase in duration of breast-feeding [24].

Endometrial and cervical safety

The LNG-IUS has a strong suppressive effect on the endometrium [16, 17]. The endometrium becomes thin and bleeding decreases. There have been preliminary reports of the LNG-IUS as a therapy for endometrial hyperplasia [26–28]. The suppressive effect on the endometrium is especially beneficial in obese women of reproductive age because of the risk of excessive endometrial proliferation leading to hyperplasia as a result of elevated estradiol production from adipose tissue. Large multicentre studies have detected no differences in cervical cytology between copper-releasing IUD and LNG-IUS users [11].
Glucose metabolism

Contraceptive options for women with insulin-dependent diabetes mellitus are limited because of concerns about potential vascular and metabolic effects associated with hormonal methods [29]. In a recent study [30], women with insulin-dependent diabetes were randomly assigned to use the LNG-IUS or copper-releasing IUD. It was found that the LNG-IUS had no adverse effect on glucose metabolism. Concern about a potential adverse effect of the LNG-IUS on glucose control is thus unwarranted.

Bone mineral density (BMD)

Progestogen-only contraception has been found to have adverse effects on bone mineral density (BMD) during long-term use. There is increasing evidence indicating a negative impact of depot medroxyprogesterone acetate on bone health in adolescents [31]. Furthermore, results suggest that low ethinylestradiol-containing (20 μg) oral contraceptive pills are unable to replace normal ovarian estradiol production and have a potentially adverse effect on bone health [31, 32]. On 17 November 2004 the FDA required a warning to be issued with regard to the long-term use of depot medroxyprogesterone acetate.

Serial samples of estradiol plasma concentrations have been measured during LNG-IUS use [33, 34]. It was found that even during amenorrhoea ovarian estradiol production was normal as judged by follicular levels in plasma [14]. Ovarian function is equal in both amenorrhoeic and menstruating LNG-IUS users [11]. A decrease in BMD or signs of osteoporosis were not even anticipated because the absence of bleeding is not caused by a lack of estradiol but by the antiproliferative action of levonorgestrel on the endometrial mucosa. A recent study by Bahamondes et al. [35] reported on the BMD of LNG-IUS users over a 7-year period. No differences in BMD were found between LNG-IUS and copper-releasing IUD users, thus supporting the earlier hypothesis.

References

5. Faundes A, Alvarez F, Diaz J. A Latin American experience with levo-
8. Pakarinen P, Toivonen J, Luukkainen T. Randomized comparison of levo-
9. Abdollahi M, Cushman M, Roseanda FR. Obesity: risk of venous throm-
busis and the interaction with coagulation factor levels and oral contra-
14. Nilsson CG, Lähteenmäki PL, Luukkainen T. Ovarian function in amen-
20. Belhadj I, Sivin I, Daz S, et al. Recovery of fertility after use of the levo-
norgestrel 20 mcg/d or Copper T 380 Ag intrauterine device. Contracep-
21. Heikkilä M. Puerperal insertion of a copper-releasing and a levo-
24. Heikkilä M, Luukkainen T. Duration of breast-feeding and development of children after insertion of a levonorgestrel-releasing intrauterine con-
26. Perino A, Quartararo P, Catena E, et al. Treatment of endometrial hyper-
27. Bahamondes L, Ribeiro-Huguet P, de Andrade KC, et al. Levonorgestrel-
Can the levonorgestrel-releasing intrauterine system (Mirena®) be used in nulliparous women?

Sarah Prager, Philip Darney
Department of Obstetrics, Gynecology and Reproductive Sciences, San Francisco General Hospital, University of California, San Francisco, CA, USA

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS), known as Mirena® (or Levonova® in Scandinavia), was first introduced in Finland in 1990. Since then, it has been approved for use in over 100 countries [1]. In multiple trials it has been shown to be a safe, effective and acceptable method of contraception, with few side effects or negative sequelae [2–4]. Its contraceptive efficacy is comparable to, if not higher than, surgical sterilization, and its use has many non-contraceptive benefits, including improvement in anaemia, menorrhagia and endometriosis, control of uterine fibroids and adenomyosis, and possible protection against and treatment of endometrial hyperplasia and cancer [5, 6].

However, most trials of the LNG-IUS and other forms of intrauterine contraception have limited enrolment to parous women. The limited data in nulliparous women, as well as misunderstandings about the relationship between intrauterine contraception and pelvic inflammatory disease (PID), have caused concerns about its use in nulliparous women. Warnings about intrauterine contraception for nulliparous women come largely from misinformation about the risk of infertility associated with intrauterine contraception, but clinicians also worry that it might be less effective and cause more side effects, making it less acceptable to nulliparous women. This article will address the use of the LNG-IUS in nulliparous women with respect to several important outcomes and hopefully dispel these concerns.

Mechanical issues

Any intrauterine device (IUD) must fit within the contours of the uterine cavity. In general, parous women of reproductive age have higher uterine volume and a greater endometrial surface area than nulliparous and nulligravid women [7]. Clinicians are concerned that a smaller cavity may increase the risk of failure due to expulsion, perforation or early discontinuation in nulliparous compared with parous women.

While studies have attempted to estimate the risk of perforation from insertion of intrauterine contraceptives, few have included nulliparous women. The rate of perforation for all women using the LNG-IUS is 0–1.3% [8], and the primary risk factor associated with perforation, lactation [9, 10], is not relevant to nulliparous women. At this time, there are not enough data on nulliparous women specifically to make a statement regarding risk of perforation with the LNG-IUS.

The risk of expulsion does not seem to be increased in nulliparous women. A multicentre international trial found that the annual expulsion rate of the LNG-IUS was 0–4.2 per hundred (the rates decreasing with increased length of use), but the trial did not include nulliparous women [8]. A Spanish trial of four different copper-releasing IUDs found no difference in expulsion rates by parity [11]. A retrospective cohort study of 129 nulliparous and 332 parous women in the Netherlands found that expulsion rates were 0–1.2% per year for the copper-releasing IUD and 0–0.2% per year for the LNG-IUS [12]. There were no statistically significant differences in expulsion rates between nulliparous and parous women. The LNG-IUS seems unlikely to have a greater risk of perforation or expulsion in nulliparous women, though there are only scant data regarding perforation risks in this population.

Efficacy and acceptability

The overall efficacy of the LNG-IUS is excellent, with rates ranging from 0 to 1.1 pregnancies per hundred woman-years of use [2, 8, 13]. A recent prospective non-comparative study evaluated efficacy by parity and found no pregnancies at 1 year in either parous or nulliparous women. In this study two different types of levonorgestrel intrauterine systems were used: the Femilis® or the Femilis® Slim (designed for use in nulliparous women) [13]. However, it is still reasonable to conclude equivalent efficacy, since in other studies of intrauterine contraception, smaller uterine size is not associated with lower efficacy [11].
Acceptability of the LNG-IUS is evaluated by continuation rate. One study found the 1-year continuation rate in nulliparous women using the LNG-IUS to be 80 per 100, which is comparable to that of multiparous women and better than the continuation rates in nulliparas taking combined oral contraceptive pills [14, 15]. A comparison of side effects experienced by nulliparous women after 1 year of using either the LNG-IUS or the combined oral contraceptive pill revealed significantly less dysmenorrhoea, intermenstrual bleeding and spotting, and significantly fewer total bleeding days in the LNG-IUS group. The LNG-IUS group also had fewer regular cycles when compared with the combined oral contraceptive group, largely due to amenorrhoea [14]. Overall satisfaction at the end of the 1-year study, as indicated by willingness to continue with the same method, was 88% in LNG-IUS users and only 68% in combined oral contraceptive users (p-value 0.003). Data about efficacy of the LNG-IUS in nulliparous women are scant; however, they are comparable to data in parous women. Acceptability in nulliparous women appears high when compared with both parous women and nulliparous users of combined oral contraceptives.

**PID and infertility risks**

Patients and providers often express concern about the possible relationship between the use of intrauterine contraception and both PID and subsequent infertility. This possible relationship is of particular concern to nulliparous women who do not yet know whether they can become pregnant. Numerous studies in the 1970s and 1980s found an increased risk of PID and infertility in users of intrauterine contraception [16, 17]. Many of these studies were subsequently reanalysed and it was found that most of the increased risk was associated with one type of intrauterine contraception no longer marketed (Dalkon Shield) and with high-risk sexual behaviour [18–20]. In fact, in many studies, the increased risk of PID was only present in the first 20 days after insertion, indicating undiagnosed cervical infection at the time of insertion. Further, many studies had methodological flaws that introduced bias into the results, such as comparing women using intrauterine contraception with those taking combined oral contraceptive pills (who have a decreased risk of PID compared with non-users) [21].

An important error in the early studies was equating nulliparity with high-risk sexual behaviour. Since young women are more likely to acquire sexually transmitted cervical infections, and because young age is associated with nulliparity, many studies erroneously concluded that the increased risk of PID and infertility was attributed to nulliparity. We now realize, based on more recent evidence, that women with high-risk sexual behaviour and sexually transmitted infections at the time of intrauterine contraception placement are at increased risk, and that age and nulliparity were ‘surrogates’ for cervical infection at the time of insertion of the contraceptive.

A case-control study in nulliparous Mexican women who were seeking treatment for primary infertility found no association between tubal infertility and past intrauterine contraceptive use. In this study, 358 women with primary infertility and documented tubal occlusion (cases) were compared with two sets of controls: 953 nulliparous women with primary infertility and no tubal occlusion and 584 primigravid women. Past use of a copper-releasing IUD was not associated with tubal occlusion when compared with either infertile women without tubal occlusion or primigravid controls (p-values 1.0 and 0.9, respectively) [22]. However, tubal infertility was associated with a past *Chlamydia* infection (as evidenced by *Chlamydia* antibodies). This study further supports an association between PID and infertility and cervical infection, not IUD use. While this study in nulliparous women evaluated the relationship between tubal infertility and copper-releasing IUD use, it is reasonable to extrapolate the findings of no association between intrauterine contraception and infertility to the LNG-IUS, for which studies have shown the expected protective effect of other hormonal contraceptives.

Not only does the LNG-IUS not increase the risk of PID, there is physiological and clinical evidence that the LNG-IUS may be protective against PID. One of the primary physiological effects of progestogen contraception is thickening of the cervical mucus, which protects against ascending genital tract infection and is the cause of decreased PID in women who use combined oral contraceptives, progestogen implants or progestogen injectables [23]. Further, a randomized controlled trial comparing the LNG-IUS with a copper-releasing IUD (Nova-T®) in parous and nulliparous women found that the cumulative 36-month rate of PID was lower in users of the LNG-IUS when compared with users of the Nova-T® (0.5 and 2.0, respectively; p < 0.013) [4], especially in women under the age of 25. Though a subanalysis in nulliparous women was not reported, the subjects include nulliparous women, making these data applicable to this population.

In spite of limited direct evidence about the relationship between infertility and LNG-IUS use in nulliparous women, we can conclude that nulliparous intrauterine contraceptive users are at no increased risk of infection and infertility over that of multiparous intrauterine contraceptive users. In fact, it is the women who have a sexually transmitted infection present in their cervix at the time of insertion who are at increased risk of PID within the first 20 days after insertion. Thus, it is important to assess each woman’s risk of infection based on her sexual behaviour (and not on parity) to screen at the time of, or prior to, insertion, and to treat cervicitis. If amplified DNA screening for *Chlamydia* or gonococcal infection is positive at the time of insertion, the intrauterine contraceptive can be left in place during treatment as long as upper tract infection does not develop [21].
Postabortal use

Between 39% and 52% of all abortions are obtained by nulliparous women [24, 25]. Most women who present for abortion have experienced a contraceptive failure and are at high risk of another, thus making them good candidates for a highly efficacious contraceptive method such as an intrauterine method. Placement of an intrauterine contraceptive immediately following an abortion is ideal, given an already dilated cervix, minimal additional discomfort for the patient, certainty that the patient is not pregnant, and peace of mind for the patient in knowing that her method is in place and requires no further intervention except for string checks. However, there has been concern that postabortal placement of an intrauterine contraceptive might lead to perforation, expulsion and infection. A Cochrane review on this topic indicated that the cumulative net probability of expulsion after second-trimester procedures is approximately 5- to 10-fold higher than the rate after first-trimester procedures for three different copper-releasing IUDs [26]. A comparison of postabortal insertion with interval insertion (3–5 weeks after procedures) found a higher expulsion rate after immediate insertion, but this difference did not reach statistical significance.

"Studies support our conclusion that it is safe to offer postabortal placement of the LNG-IUS to nulliparous women."

A trial that compared postabortal insertion of the LNG-IUS with insertion of various copper-releasing IUDs found significantly fewer pregnancies after placement of the LNG-IUS [26]. When compared with historical controls, overall rates of PID, perforation and other complications after postabortal insertion were similar [26]. Nulliparous women were included in a few of these studies, but analyses of associations between nulliparity and complications or failure of the LNG-IUS were not reported. One observational study of LNG-IUS insertion in 20 nulliparous women following surgical abortion found that all the subjects who completed the study continued with the LNG-IUS, and therefore concluded that it is an acceptable method of contraception and could be offered to young, single, nulliparous women after abortion [27]. In general, these studies support our conclusion that it is safe to offer postabortal placement of the LNG-IUS to nulliparous women.

Conclusion

Although we need more information about the benefits and risks of LNG-IUS use in nulliparous women, there are extensive data about the efficacy and safety of the device and of other currently available intrauterine contraceptive methods. In order to provide young women, many of whom are nulliparous, with the most effective methods of contraception we feel that the LNG-IUS may be offered to nulliparous women, since it appears to be both safe and extremely efficacious.

References

2. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Novo T) IUDs during five years of use: a randomized compara-
13. Wiltshire C. Ease of insertion, contraceptive efficacy and safety of new T-shaped levonorgestrel-releasing intrauterine systems. Contracep-
14. Toivonen J. Clinical performance of a levonorgestrel-releasing intrauter-
ine system and oral contraceptives in young nulliparous women: a compara-
17. World Health Organization Task Force on Intrauterine Devices, Special Programme of Research, Development and Research Training in Human Reproduction. PID associated with fertility regulation agents. Contracep-
tion 1984; 30: 1–21.
18. Lee NC, Rubin GL, Borucki R. The intrauterine device and pelvic inflam-
25. Bartley J, Tonga S, Everington D, Bainl DT. Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 con-
27. Li CF, Lee SS, Pun TC. A pilot study on the acceptability of levonorgestrel-
The levonorgestrel-releasing intrauterine system (Mirena®) as an alternative to tubal occlusion

Ian Milsom

Department of Obstetrics and Gynaecology, Sahlgrenska Academy at Göteborg University and Sahlgrenska University Hospital, Göteborg, Sweden

Tubal occlusion

Sterilization by tubal occlusion is a common form of contraception in many countries where it accounts for a large proportion of contraceptive use in women over 30 years of age. In the United States male/female sterilization accounts for more than 40% of contraceptive use (Figure 1) [1] and similar sterilization rates have been reported from several European countries [2, 3].

As tubal occlusion is intended to be a permanent form of sterilization, it is considered important that an adequate time interval elapses between counselling and the performance of the surgical procedure in order to ensure a well-considered decision. Thus, tubal occlusion is not a method that can be readily used in an acute situation, as it is important that the woman carefully contemplates her decision before undergoing the surgical procedure [4].

Tubal sterilization is considered to be a highly effective form of contraception, but there is nevertheless a risk of pregnancy, which varies according to the sterilization technique used [5]. The cumulative 10-year probability of pregnancy has been reported to be highest after clip sterilization (36.5/1000 procedures) and lowest after unipolar coagulation (7.5/1000) and postpartum partial salpingectomy (7.5/1000). The cumulative risk of pregnancy has been reported to be highest among women sterilized at a younger age with bipolar coagulation (54.3/1000) and clip application (52.1/1000) [5].

Although a relatively simple procedure, like all surgical procedures it is associated with a risk of complications during surgery. The lowest rate of complications has been reported with laparoscopy (0.9–1.7%); laparotomy has approximately twice the risk of complications [4]. The most common complication arises when there is a need to convert a laparoscopic procedure to a laparotomy because of an inability to complete the sterilization laparoscopically, with most studies describing a 1% incidence. Burns can occur from accidental electrocoagulation resulting in late perforation and peritonitis. Both with laparoscopy and laparotomy there is a risk of wound infections and/or wound dehiscence (Table I). The mortality rate has been reported to be 3.6–4.0 per 100,000 operations, half of which is due to complications from general anaesthesia and the other half to the operative procedure [4].

“Despite counselling, a large proportion of women regret tubal sterilization. The best predictor of regret and a desire for re-anastomosis is age.”

In addition, it has also been reported that, despite counselling, a large proportion of women regret the...
procedure [4]. It has been shown that the best predictor of regret and a desire for re-anastomosis is age: the younger the woman’s age at sterilization the greater the risk of regret.

There are also reports that the procedure may cause more long-term somatic symptoms such as pain and bleeding disturbances [4–7]. The occurrence of menstrual disturbances has been shown to vary according to the type of procedure performed. Adverse menstrual changes occurred significantly more often after cauterization and with the Pomeroy technique [6].

The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®)

The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) has been shown to be a highly effective form of long-term reversible contraception (Table II). In a large European randomized multicentre study [9], the efficacy of the LNG-IUS was compared with that of a copper-releasing intrauterine device (IUD; Nova-T®). The cumulative 5-year gross pregnancy rate was 5.9 for the copper-releasing IUD and 0.5 for the LNG-IUS. Thus, the contraceptive efficacy of the LNG-IUS does not differ greatly from that reported after female sterilization.

Women who have an LNG-IUS fitted often experience irregular bleeding after insertion of the device. However, the bleeding is usually scanty and in many cases results in amenorrhoea after a variable period of time. Some women experience hormonal side effects for a short period of time after insertion such as breast tenderness and nausea. The cumulative gross termination rates at 60 months reported in the prospective comparison between the LNG-IUS and a copper-releasing IUD are shown in Table III.

There are also several non-contraceptive benefits with the LNG-IUS such as a reduction in menstrual blood loss [12] and dysmenorrhoea [12]. In a study comparing the LNG-IUS with a copper-releasing IUD it was shown that women fitted with an LNG-IUS had an increase in haemoglobin concentration (+2 g/l), whereas women fitted with a copper-releasing IUD had a decrease in haemoglobin (−3 g/l) following IUD insertion [12]. Return to fertility after removal of the LNG-IUS has also been studied and, although the system induces suppression of the endometrium and in many cases amenorrhoea, the return to fertility was no different from that in women who had been fitted with a copper-releasing IUD [13].

Thus, it is apparent from these data that the LNG-IUS is an equally effective contraceptive method as tubal sterilization but with the advantage of being reversible. In addition, many women also experience the advantage of being amenorrhoeic. In a long-term

---

**Table I:** Complications of female sterilization [4].

<table>
<thead>
<tr>
<th>Complication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>At laparoscopy</td>
<td></td>
</tr>
<tr>
<td>Mesosalpingeal tears</td>
<td>0.3</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.3</td>
</tr>
<tr>
<td>Bowel burns, which may result in late perforation and peritonitis</td>
<td>≤0.6</td>
</tr>
<tr>
<td>Necessary to convert to laparotomy</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Wound infections or dehiscence</td>
<td>1.0</td>
</tr>
<tr>
<td>Total complication rate</td>
<td>0.9–1.7</td>
</tr>
<tr>
<td>At laparotomy</td>
<td></td>
</tr>
<tr>
<td>Total complication rate</td>
<td>1.7–3.4</td>
</tr>
<tr>
<td>Late sequelae</td>
<td></td>
</tr>
<tr>
<td>Regret 2 years post-sterilization</td>
<td>2.7</td>
</tr>
</tbody>
</table>

**Table II:** Gross cumulative pregnancy rates in four randomized clinical trials comparing the LNG-IUS with different copper-releasing IUDs.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Women (n)</th>
<th>Follow-up (years)</th>
<th>Pregnancy rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson et al. [8]</td>
<td>LNG-IUS</td>
<td>321</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Copper IUD</td>
<td>321</td>
<td>2</td>
</tr>
<tr>
<td>Andersson et al. [9]</td>
<td>LNG-IUS</td>
<td>1821</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Copper IUD</td>
<td>937</td>
<td>5</td>
</tr>
<tr>
<td>Sivin et al. [10]</td>
<td>LNG-IUS</td>
<td>1124</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Copper IUD</td>
<td>1121</td>
<td>5</td>
</tr>
<tr>
<td>Indian Council of Medical Research [11]</td>
<td>LNG-IUS</td>
<td>475</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Copper IUD</td>
<td>500</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table III:** Cumulative gross termination rates at 60 months reported in a prospective randomized trial comparing the LNG-IUS with a copper-releasing IUD (Nova-T®) [9].

<table>
<thead>
<tr>
<th></th>
<th>Nova-T®</th>
<th>LNG-IUS</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>5.9</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Expulsion</td>
<td>6.7</td>
<td>5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding problems</td>
<td>20.7</td>
<td>13.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>0</td>
<td>6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>5.8</td>
<td>5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hormonal side effects</td>
<td>2.0</td>
<td>11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>2.2</td>
<td>0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Other medical</td>
<td>10.6</td>
<td>7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Personal</td>
<td>21.7</td>
<td>19.6</td>
<td>NS</td>
</tr>
<tr>
<td>Continuation rate</td>
<td>44.5</td>
<td>46.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
study of the LNG-IUS over 12 years as many as 60% of the women were amenorrhoeic and it was shown to be a safe and effective method of contraception, providing the women at the same time with a prolonged relief of menstrual problems [14]. In the age group where tubal sterilization is most frequently used, a significant proportion of women suffer from menorrhagia, but tubal sterilization does not protect these women from this bleeding disturbance. In contrast, the LNG-IUS offers the advantage of being a simultaneous form of treatment for heavy menstrual bleeding [15] as well as offering effective contraception.

"In contrast to tubal occlusion the LNG-IUS provides a reversible form of contraception with the added advantage for many women of reduced menstrual blood loss or even amenorrhoea."

The cost-effectiveness of various contraceptive techniques has been studied and the LNG-IUS has been shown to be one of the most cost-effective contraceptives available [16]. According to Chiou et al. [16], the effectiveness of tubal ligation and the LNG-IUS was comparable, but the LNG-IUS was less expensive (Figure 2).

At present a large percentage of women in the United States and Europe rely on sterilization as their method of contraception. According to a cost-effectiveness analysis performed by Chiou et al. [16], if these women utilized the LNG-IUS instead there would be a considerable economic saving with approximately the same contraceptive efficacy.

**Conclusion**

The LNG-IUS is a highly effective form of contraception, with a long-term efficacy comparable to that of tubal occlusion. After insertion of the device many women experience irregular bleeding and some experience hormonal side effects. In contrast to tubal occlusion the LNG-IUS provides a reversible form of contraception with the added advantage for many women of reduced menstrual blood loss or even amenorrhoea. This is particularly important for women in the later stages of the fertile period where menorrhagia is more common. The LNG-IUS is, in addition, a cost-effective form of long-term contraception that has been reported to be superior to that reported after tubal sterilization.

**References**

Introduction

There are numerous reports in the literature on the use of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) for contraception and the treatment of gynaecological disorders. The first reports of its therapeutic effect on menorrhagia came from Europe. However, use of the LNG-IUS has enormous potential to improve women’s health in developing countries, where protection against pregnancies and reproductive health are both important to quality of life. The LNG-IUS is a contraceptive method that can effectively fulfil both functions.

Studies in Europe

As the LNG-IUS was first developed in Finland for contraceptive purposes, the device has been widely used in European countries such as Finland, Sweden, the Netherlands and the UK.

The therapeutic effect of the LNG-IUS in the treatment of menorrhagia was carefully evaluated in a Swedish study [1] which measured menstrual blood loss (MBL) before and after insertion of the device and in comparison with copper-bearing intrauterine devices and other medical treatments. Andersson and Rybo [1] studied 20 healthy parous women with regular periods and MBL >80 ml who were treated with the LNG-IUS. MBL was measured at 3, 6 and 12 months after insertion of the device. A significant reduction in MBL of 86% at 3 months and 97% at 12 months was reported and blood haemoglobin and serum ferritin were significantly increased.

In another randomized study comparing the LNG-IUS with crossover oral treatment with flurbiprofen and tranexamic acid in 35 women with idiopathic menorrhagia [2], the LNG-IUS was inserted for 12 months and flurbiprofen and tranexamic acid were used for 2 months each. MBL decreased by 21% with flurbiprofen and by 44% with tranexamic acid, but with the LNG-IUS, MBL was reduced by 82% after 3 months and by 96% after 12 months. This difference was highly significant.

A study in the Netherlands by Scholten [3] on 11 women for 12 months showed a similar reduction in MBL and an increase in haemoglobin and serum ferritin.

Studies in developing countries

The LNG-IUS is not widely used for the treatment of menorrhagia in developing countries except in China and Brazil.

China

The device was first introduced in China as a contraceptive method in 1986. Many studies on clinical performance [4], ovarian function [5, 6] and the endometrium [7] were subsequently carried out. Although all the studies were performed in normal healthy women requesting contraception, the results provided a good insight into the benefits of the LNG-IUS and its mechanism of action, which highlighted its potential in the treatment of menorrhagia.

The earliest clinical trial to explore the efficacy and acceptability of the LNG-IUS in the treatment of menorrhagia was carried out in 10 Chinese women in Hong Kong in 1995 [8]. Over a period of 129 patient-months there was a 54%, 87% and 95% reduction in MBL after 1, 3 and 6 months of treatment, respectively. The reduction was highly significant. There was a median increase in menstrual cycle length of 12 days in 9 months, and 15% of the cycles were longer than 60 days. Most bleeding (76%) was in the form of spotting. These menstrual changes were acceptable to the women, who preferred the device to hysterectomy.

Studies of the treatment of idiopathic menorrhagia were begun in Beijing in 1999 [9]. A 3-year protocol was designed with the objective of investigating the effect of the LNG-IUS in the treatment of idiopathic menorrhagia among Chinese women. Thirty-four patients aged 27–43 years with regular menstrual cycles and heavy bleeding (>80 ml) were recruited. The patients were followed up at 3-monthly intervals for the first year and then annually for 3 years. MBL, blood haemoglobin and serum ferritin were measured before and after insertion at 6, 12, 24 and 36 months.
A total of 1125 post-insertion patient-months were assessed. No intrauterine or extrauterine pregnancies occurred during the 3-year follow-up period. There were two complete expulsions: one during the first month and the other on the second day after insertion due to heavy bleeding. Two partial expulsions were observed on pelvic examination: the lower end of the vertical stem was seen to protrude from the cervical os at 6-month and 15-month check-ups. The devices were removed by the attending doctor. Two patients were lost to follow-up when they moved away from the area. There were two premature removals at 7 months due to prolonged spotting and fatigue, and another at 16 months due to persistent amenorrhoea lasting 7 months.

The main outcome results were changes in MBL, which reduced by 78.7%, 83.8%, 97.7% and 85.0% at 6, 12, 24 and 36 months, respectively. Haemoglobin and serum ferritin increased between pre- and post-insertion. The differences were highly significant. The results are shown in Table I. The reduction in MBL in each patient during the course of 3 years is shown in Figure 1.

Due to the local effect of progestogens on the endometrium, the prominent feature of the menstrual pattern is amenorrhoea and irregular spotting. Almost one-third of the patients experienced amenorrhoea after 3 months of treatment, which lasted in some cases for more than 6 months. Irregular spotting in the first 3 months was also a frequent occurrence. Measurement of the endocrinological profile during the menstrual cycle showed no or slight suppression of ovarian function, even in patients with amenorrhoea.

Slight nausea and breast tenderness were experienced by a few patients. No serious hormonal side effects occurred and no medication was required.

Brazil
The LNG-IUS was first used for contraception in 256 women in Campinas in 1998. A pilot study of the use of the LNG-IUS in 44 women with menorrhagia was published in 2002 [10]. Menstrual patterns were assessed subjectively by the patients and haemoglobin was measured at 3, 6, 9 and 12 months. In the first 3 months spotting was the most common feature, but after 6, 9 and 12 months the majority of women presented with amenorrhoea or oligomenorrhoea. There were six expulsions and one request for removal due to spotting. Haemoglobin levels increased significantly. The overall continuation rate at 12 months was 70.5%. The authors concluded that the LNG-IUS was a good alternative treatment in 75% of Brazilian women with menorrhagia who were either contraindicated for or refused hysterectomy or endometrial ablation.

Health benefits and socioeconomic implications
The LNG-IUS in the treatment of menorrhagia is a good option amongst the array of available medical and surgical treatments. This is particularly true in developing countries, where women are often in poor health and afraid of operational procedures. Chinese women would first choose traditional medicine to treat the bleeding and turn to surgery only as a last resort. The introduction of the LNG-IUS in recent years has offered these women an alternative method. It not only decreases MBL but also increases haemoglobin and serum ferritin, which is essential to women’s health.

Table I: Mean (SD) changes in MBL, haemoglobin and serum ferritin before and after LNG-IUS insertion. (Data from [9].)

<table>
<thead>
<tr>
<th></th>
<th>MBL*</th>
<th>Haemoglobin</th>
<th>Serum ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ml</td>
<td>n</td>
</tr>
<tr>
<td>Before insertion</td>
<td>34</td>
<td>124.2 ± 42.9</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>121.5 ± 10.2</td>
<td>33</td>
</tr>
<tr>
<td>After insertion (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>130.3 ± 9.5</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>132.0 ± 9.8</td>
<td>27</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>133.4 ± 8.7</td>
<td>27</td>
</tr>
<tr>
<td>24</td>
<td>26</td>
<td>138.7 ± 7.5</td>
<td>25</td>
</tr>
<tr>
<td>36</td>
<td>24</td>
<td>133.5 ± 6.6</td>
<td>23</td>
</tr>
</tbody>
</table>

p < 0.0001 throughout, except for * p < 0.001.
*Many cases with amenorrhoea or scanty spotting could not be measured.
Treatment with the LNG-IUS has special implications for women living in rural areas or on a low income: the LNG-IUS costs much less than hysterectomy or even endometrial resection or ablation. In China, the LNG-IUS, including all medical care services before and after insertion, costs about six times less than hysterectomy. As menorrhagia is one of the most common gynaecological disorders, the reduction in surgical procedures and in potential blood transfusions contributes considerably to reducing the medical burden of a family or a community.

“Unfortunately the benefits of LNG-IUS use in the developing world are not well recognized. Dissemination of information about its health benefits and socioeconomic implications in the treatment of menorrhagia is therefore essential.”

Unfortunately the benefits of LNG-IUS use in the developing world are not well recognized. Dissemination of information about its health benefits and socioeconomic implications in the treatment of menorrhagia is therefore essential.

The levonorgestrel-releasing intrauterine system (Mirena®) in the treatment of leiomyoma-related bleeding

Vera Halpern¹, Marina Tarasova²

¹Family Health International, Research Triangle Park, NC, USA; ²Ott Institute of Obstetrics and Gynaecology, St Petersburg, Russia

Introduction

Uterine leiomyomas are the most common benign pelvic tumours found in women. Data on the prevalence of uterine leiomyomas vary greatly, with some studies reporting a prevalence as high as 70% among premenopausal women [1]. Peak incidence occurs in women between 35 and 40 years old, when clinical signs are most likely to manifest. Although leiomyomas are often asymptomatic, approximately 20–40% produce symptoms, leading patients to seek therapy [2].

Almost one-third of women with uterine leiomyomas experience excessive or prolonged menstrual bleeding [3]. Menorrhagia associated with uterine leiomyomas can impair social and sexual activities and lead to lost work time, increased cost of sanitary
protection and the need for medical care [4]. Besides being troublesome, bleeding from leiomyomas can result in severe, sometimes life-threatening, anaemia [5].

**Approaches to the treatment of uterine leiomyomas**

Current approaches to dealing with abnormal uterine bleeding associated with leiomyomas fall into two broad categories. The first is surgical therapy, which ranges from traditional hysterectomy to endoscopic uterine-sparing procedures [6]. Hysterectomy for leiomyoma-related menorrhagia is highly successful. However, the existing data demonstrate that in at least a third of all surgical interventions a normal uterus is removed [7]. Furthermore, this option is unacceptable for women who are considering having children. As opposed to the permanent relief from heavy menstrual bleeding provided by hysterectomy, less invasive surgical interventions such as uterine artery embolization or myomectomy may require further invasive treatment [8, 9].

*“Uterine leiomyomas are the most common benign pelvic tumours found in women.”*

The second strategy for the management of leiomyoma-related bleeding is medically induced suppression of the endometrium. Despite the long-standing appeal of medical therapy, use of agents such as progesterone, gestrinone and danazol has not been successful [2, 10]. Currently, few drugs are known to effectively reduce the heavy menstrual bleeding associated with these tumours.

Administration of long-acting gonadotropin-releasing hormone (GnRH) analogues as well as the antiprogestogen mifepristone profoundly reduces menstrual bleeding and thus normalizes haematological indices and improves anaemia [11, 12]. Unfortunately, after the cessation of GnRH agonist therapy, the uterus and leiomyoma rapidly return to their pretreatment volume; menses return 4–10 weeks after cessation of therapy [13, 14]. The long-term administration of GnRH agonists is limited by bone loss [15] and by the high cost of the drug. The major concerns about long-term administration of antiprogestogens are the possible induction of endometrial hyperplasia and transitory increase in liver enzymes, although data on the long-term safety of mifepristone are scant and conflicting [16, 17].

**Studies with the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) in leiomyoma-related bleeding**

The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) provides a broad spectrum of non-contraceptive health benefits [18], including possible treatment of leiomyoma and related symptoms (Table I). The exact mechanism of the therapeutic effect of the LNG-IUS is unknown. By rendering the endometrium inactive and insensitive to the prolifer-

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design and sample size</th>
<th>Study duration (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer &amp; Ikomi, 1994 [19]</td>
<td>Prospective pilot study of 5 women with menorrhagia treated with intrauterine progesterone device</td>
<td>6–18</td>
<td>Reduction in MBL</td>
</tr>
<tr>
<td>Starczewski &amp; Iwanicki, 2000 [21]</td>
<td>Prospective non-comparative study of 12 women with severe menstrual bleeding fitted with the LNG-IUS</td>
<td>6–12</td>
<td>Reduction in MBL, Normalization of Hb</td>
</tr>
<tr>
<td>Mercorio et al., 2003 [22]</td>
<td>Observational study of 19 women with recurrent menorrhagia fitted with the LNG-IUS</td>
<td>12</td>
<td>Reduction in MBL, Decrease in Hb, 74% reported persistent menorrhagia at the end of the study</td>
</tr>
<tr>
<td>Grigorieva et al., 2003 [23]</td>
<td>Prospective non-comparative study of 67 women with uterine leiomyomas fitted with the LNG-IUS</td>
<td>12</td>
<td>Reduction in MBL, Increase in Hb and ferritin 40% reported amenorrhoea at the end of the study</td>
</tr>
<tr>
<td>Rosa e Silva et al., 2005 [24]</td>
<td>Descriptive case series of 10 women with increased uterine bleeding fitted with the LNG-IUS</td>
<td>6</td>
<td>Reduction in MBL, Normalization of Hb and haematocrit</td>
</tr>
<tr>
<td>Soysal &amp; Soysal, 2005 [25]</td>
<td>Prospective, historically controlled study of 32 menorrhagic women fitted with the LNG-IUS and 32 treated with thermal balloon ablation</td>
<td>12</td>
<td>Similar reduction in MBL, Similar increase in Hb</td>
</tr>
</tbody>
</table>

MBL, Menstrual blood loss; Hb, haemoglobin.
From the American Society for Reproductive Medicine.)

Blood Loss Assessment Chart. (Reproduced from [23] with permission)

In spite of a large number of studies investigating the effect of the LNG-IUS on idiopathic menorrhagia [29, 30], few have specifically looked into the therapeutic benefits of the LNG-IUS in women with uterine leiomyomas. Although limited, the existing data suggest that the LNG-IUS is a promising treatment for women with heavy bleeding associated with leiomyomas. Researchers from Poland inserted the LNG-IUS in 12 women with uterine leiomyomas and severe menstrual bleeding and followed them for 6–12 months [21]. Amenorrhoea was reported by 50% of women with intramural tumours after 12 weeks, and the remainder had scanty bleeding. Six months after insertion of the device, haemoglobin levels were normal in 11 women.

The biggest case series to date found a dramatic reduction in menstrual blood loss accompanied by an improvement in haematological indices in 67 women with uterine leiomyomas treated with the LNG-IUS for 1 year [23]. A profound reduction in menstrual blood loss occurred within 3 months of insertion (Figure 1) and was accompanied by significant increases in blood haemoglobin and serum ferritin levels. Within 3 months of insertion the mean haemoglobin value significantly increased (13.2 ± 1.3 g/dl vs. 12.6 ± 1.2 g/dl; p < 0.001) and remained significantly higher than baseline values at 6 months (13.7 ± 1.0 g/dl; p < 0.001) and 12 months (13.6 ± 0.9 g/dl; p < 0.001). Serum ferritin levels changed little by 3 months (25 ± 22 ng/ml vs. 24 ± 23 ng/ml) but showed a significant increase at 6 and 12 months (32 ± 24 ng/ml; p < 0.001; 41 ± 28 ng/ml; p < 0.001, respectively). Eighteen out of 19 women (95%) who were anaemic at the start of the study were no longer anaemic at 12 months. Moreover, 40% of participants had amenorrhoea at the end of the study. The finding that the LNG-IUS effectively treated iron-deficiency anaemia in women with menorrhagia associated with leiomyomas was in accord with studies comparing the effectiveness of the LNG-IUS with operative treatments of menorrhagia [31, 32]. Only four women with uterine leiomyomas (6%) expelled the device during the study by Grigorieva et al. [23]. This is similar to the 4% expulsion rate reported by Diaz et al. [33] among 1101 women without pre-existing gynaecological conditions fitted with the LNG-IUS for contraception only.

Soysal & Soysal [25] were the first to evaluate the use of the LNG-IUS in menorrhagic patients with submucous leiomyomas. The authors compared the device with the results of thermal balloon ablation chosen as a historic control. The LNG-IUS was as effective as the surgical procedure in treating the excessive bleeding and related anaemia.

Rosa e Silva et al. [24] inserted the LNG-IUS in 10 patients with uterine myomas complaining of increased uterine bleeding. They observed a significant reduction in bleeding and improvement of the haematological indices following 6 months of LNG-IUS use.

Most of these studies reported no LNG-IUS-induced side effects other than abnormal bleeding. Only Grigorieva et al. [23] documented breast tenderness as the most frequently encountered side effect other than irregular spotting.

Figure 1: Estimated menstrual blood loss (mean ± SD) before and after insertion of the LNG-IUS (*p < 0.001 vs. baseline). PBAC, Pictorial Blood Loss Assessment Chart. (Reproduced from [23] with permission from the American Society for Reproductive Medicine.)

“According to WHO guidelines for contraceptive use, only pre-existing uterine fibroids that distort the uterine cavity contraindicate the method.”

A weakness of most of these studies is the lack of a control group. Despite their uncontrolled nature, the observed changes in bleeding patterns and haematological indices are likely to be the result of the LNG-IUS. Given the natural history of untreated leiomyomas in women of reproductive age, the likelihood of such dramatic improvements in bleeding occurring spontaneously is small.

Some researchers expressed concerns in the past about the use of the LNG-IUS by women with uterine...
leiomyomas reporting higher rates of expulsion in the presence of uterine fibroids, uterine enlargement, heavy bleeding and anaemia [34]. Mercorio et al. [22] found that menorrhagia persisted in 74% of patients after 1 year of LNG-IUS use. These authors concluded that the LNG-IUS should not be considered in the presence of a large myomatous uterus. While these concerns may warrant further research, they should not deter clinicians from using the intrauterine system in women with uterine leiomyomas. Each clinical case, however, requires careful individual assessment. The LNG-IUS should not be a substitute for surgical treatment where surgery is an acceptable option and will clearly provide a better clinical outcome. According to WHO guidelines for contraceptive use [35], only pre-existing uterine fibroids that distort the uterine cavity contraindicate the method. Until more extensive experience with the LNG-IUS in women with leiomyomas is available, compliance with the WHO eligibility criteria for intrauterine contraceptives in women with uterine leiomyomas seems prudent.

Conclusion
Uterine leiomyomas pose an enormous global health problem. A safe, effective, reversible, long-term, non-surgical treatment for symptomatic leiomyomas would be of considerable clinical and public health importance. The LNG-IUS has strong potential for providing effective treatment of the excessive uterine bleeding associated with leiomyomas. That the available evidence of LNG-IUS use in women with uterine leiomyomas continues to be based primarily on retrospective or prospective non-comparative research indicates a long-standing need for a well-designed comparative study.

References
Quality of life and cost-effectiveness of the levonorgestrel-releasing intrauterine system (Mirena®) and hysterectomy in menorrhagia

Ritva Hurskainen

Department of Obstetrics and Gynaecology, Hyvinkää Hospital, Hyvinkää, Finland (ritva.hurskainen@hus.fi)

Introduction

Menorrhagia, usually defined as heavy menstrual bleeding over several consecutive cycles, has a significant impact on many women’s lives. Rapid developments in medical technology have delivered new management strategies for menorrhagia, prompting clinicians to consider the cost and effectiveness of the treatments available. Accurate information on the cost-effectiveness of the different treatment options would ensure the best health outcomes from the available resources. Menorrhagia is usually a benign disorder and treatment is aimed at improving health-related quality of life (HRQOL). Self-reported HRQOL has been regarded as the most reliable key variable of effectiveness. There are many generic and disease-specific tools for assessing HRQOL, but few of them have a single index value that can be used for economic evaluation. Studies of the cost and effectiveness of the different treatment modalities for menorrhagia are rare.

Although hysterectomy is by definition more effective than other treatment modalities for menorrhagia, the morbidity and complication rates associated with hysterectomy cannot be ignored [1]. The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) offers a truly effective and reversible treatment modality for menorrhagia. A number of recent studies have reported improvements in HRQOL after hysterectomy [2–5] and insertion of the LNG-IUS [6], but few have reported on the cost-effectiveness of these two treatments.

Effectiveness of the LNG-IUS and hysterectomy

LNG-IUS

Traditionally, evaluation of the effectiveness of medical treatments has relied upon measures of morbidity (based on clinical, radiological and laboratory tests) and mortality. The most commonly used outcome reflecting the effectiveness of menorrhagia treatments is the reduction in menstrual blood loss (MBL). However, menorrhagia may have a strong effect on the quality of women’s lives, including both physical and psychological health. Social and working abilities may be disrupted, and some women report adverse effects in their family life causing considerable strain on family relationships. Women seek professional help for their menstrual problems mostly because of the deleterious effect on their quality of life.

To use millilitres of reduced MBL as the only indicator of effectiveness gives a poor estimate of how women feel after treatment. A more appropriate outcome indicator is HRQOL. The tools assessing HRQOL are normally categorized as generic or disease-specific. Generic measures have increased in popularity, because they enable comparison between different health problems. Disease-specific instruments give more accurate information about a specific health problem; thus there are clear reasons for using both types of instrument side by side.

In evaluating the success of treatment of menorrhagia the most commonly used validated HRQOL measurement is the Short Form 36 (SF 36). This is a shortened version of a battery of 149 health status questions developed and tested on a large population. It uses eight scales to measure three aspects of health: functional status, well-being and general evaluation of health. The five-dimensional EuroQol (EQ-5D) is an HRQOL instrument which gives a single number score that in a comprehensive and valid way reflects the total change in HRQOL. It can be used to calculate quality-adjusted life years (QALYs). It includes five dimensions: mobility, self-care, usual activities, pain and mood.
To understand the effectiveness of the LNG-IUS and hysterectomy with regard to HRQOL we must be aware of the clinical effects of these treatments. Controlled trials supported by evidence from observational studies show that the LNG-IUS can significantly reduce MBL (up to 94% after 3 months) and is well accepted by most women [7]. The device also provides contraception comparable to that of sterilization, with fertility returning when the system is removed [8]. It also offers other therapeutic effects that can improve HRQOL. Reduction in dysmenorrhea has been reported in numerous LNG-IUS trials [9, 10] as well as reduction in premenstrual symptoms [11]. There is also preliminary evidence that the LNG-IUS may be therapeutic in women with fibroids [12, 13], endometriosis [14–16] and adenomyosis [17], which are often connected with heavy bleeding. The LNG-IUS releases 20 μg levonorgestrel per day, resulting in low serum concentrations. However, some hormonal side effects are possible especially in the first 3 months. The LNG-IUS frequently causes irregular vaginal bleeding or spotting and some women experience breast tenderness and bloating [18], all of which increase the failure rate. Most side effects, however, resolve within a relatively short time.

Hysterectomy

Hysterectomy is one of the most common surgeries performed on women and has been the standard treatment for menorrhagia for many decades. Although hysterectomy is a successful operation with high levels of patient satisfaction, there is a risk of complications. Mortality is relatively low (1–2/1000 operations) [19, 20], but the risk of lesser complications is quite high, occurring in one-third of procedures [5, 21, 22]. Hysterectomy may impair ovarian function and cause early menopausal symptoms [23]. Constipation, symptoms arising from adhesions and urinary problems are all connected with the procedure [24, 25].

Effectiveness comparison

Treatment of menorrhagia with hysterectomy and the LNG-IUS is the subject of two Cochrane reviews which evaluated among other effects the impact of menorrhagia treatments on HRQOL [4, 6]. In four trials patients in the medical arm received the LNG-IUS and those in the surgery arm underwent transcervical resection of the endometrium (TCRE), thermal balloon ablation or hysterectomy. At 1 year, there was no statistically significant difference between the study arms in satisfaction rates or quality of life (measured by SF 36 or EQ-5D), but endometrial destruction was less likely to cause adverse effects than the LNG-IUS (OR 0.24, 95% CI 0.11–0.49). Hysterectomy stopped all bleeding but caused serious complications for some women. The LNG-IUS was superior to oralmedication.

Economic studies of the LNG-IUS and hysterectomy

Randomized health economic studies of menorrhagia are scarce. There are no economic evaluations comparing medical treatments. Five publications, from three randomized trials, compared the overall cost of endometrial resection vs. hysterectomy [2, 26–29]. All these trials reported that endometrial resection cost less than hysterectomy in a 1-year follow-up. The difference in the cost gap narrowed over time because of the re-treatment rate for women who had undergone endometrial resection. Based on 4 months’ follow-up [29] the cost of resection was 53% of that of hysterectomy (TCRE £560, hysterectomy £1060); after 12 months’ follow-up the respective value was 76% (£1001 and £1315) [28]; after 2.8 years of follow-up it was 71% (£790 and £1110) [2]; and at 4 years it was 93% (£1231 and £1332) [26].

Only one randomized large-scale study with 236 women compared the cost-effectiveness of the LNG-IUS vs. hysterectomy over 5 years [22]. This study included costs of health care, medication and lost productivity. The total direct health care cost per patient after 1 year was US $1074 in the LNG-IUS group and US $2489 in the hysterectomy group. When lost productivity was added, the total cost per woman in the LNG-IUS group was US $1530 and in the hysterectomy group US $4222 [30]. Although 42% of women assigned to the LNG-IUS eventually underwent hysterectomy, the discounted direct cost after 5 years was US $1892 with the LNG-IUS and US $2787 with hysterectomy; the total costs were US $2817 and US $4660, respectively, at 2001 prices.

HRQOL and psychosocial well-being improved significantly in both groups and there was no difference between the groups. The cost per QALY was US $6190 per woman in the LNG-IUS group and US $9017 per woman in the hysterectomy group (Hurskainen R. Unpublished data), which shows that treatment of menorrhagia is significantly more cost-effective with the LNG-IUS than with hysterectomy.
Conclusion

Heavy menstrual bleeding is a common complaint, which causes much inconvenience as well as physical, mental and emotional problems to many women. It has a prominent effect on HRQOL [30]. Many studies have shown that treatment of menorrhagia significantly improves quality of life (Figure 1) [1, 22, 31–34]. However, increasing healthcare costs are a worldwide phenomenon and there is a clear need for strategies that produce net cost savings. Data from the 1970s to the 1990s suggest that menstrual complaints are on the increase [22] and call for greater resources. Most of this increase is in menorrhagia.

In western countries, about 5% of women of reproductive age seek help annually for menorrhagia [35]. Hysterectomy is one of the most frequently performed major surgical procedures for menorrhagia and therefore the consequences concern a large number of women and a large amount of money. The LNG-IUS seems to offer a good and reversible alternative to hysterectomy. The cost-effectiveness of the LNG-IUS seems to be significantly better than that of hysterectomy. Over 5 years the LNG-IUS offers the same improvement in quality of life as hysterectomy, but the costs are 40% lower [22]. In Finland about 10,000 hysterectomies are performed each year. At least 3000 of these are due to menorrhagia, which could also be treated with the LNG-IUS. If all those women were hysterectomized, the cost of treatment (including sick leave and complications) would be about €14 million. If all those women were first treated with the LNG-IUS and then only those who were not satisfied (42%) were hysterectomized, the treatment cost would be about €8.5 million. By adopting the latter strategy we could save at least €5.5 million without impairing the HRQOL of menorrhagic women. These data are from a study by Hurskainen et al. [22], which included patients who were referred to hospital for hysterectomy. The savings could be even greater if the LNG-IUS were inserted in primary care before referral. It would be a straightforward matter to issue care guidelines recommending LNG-IUS insertion before referral to a specialist if there are no contraindications. Many women prefer less invasive surgical treatment even when they are aware that the success of the treatment is not always assured [36]. The majority of menorrhagic women scheduled for endometrial ablation or LNG-IUS insertion are inclined to risk a 50% likelihood of treatment failure to avoid a hysterectomy [36].

References

Endometriosis affects almost 10% of women of reproductive age. Seventy to ninety percent of women with chronic pelvic pain, dysmenorrhea, dyspareunia, infertility or menstrual disturbances have endometriosis [1], a disease that impairs their quality of life [2].

Gonadotropin-releasing hormone analogues (GnRHa)

Surgical and medical therapies have been used to treat chronic pelvic pain associated with endometriosis, and gonadotropin-releasing hormone analogues (GnRHa) are the gold standard drug treatment. Treatment is based on reducing lesions or suppressing ovarian estrogen production.

However, adherence and long-term treatment continue to represent challenges in the management of endometriosis. Because of the profound hypoestrogenism provoked by GnRHa, their use is limited to 6 months, although longer treatment with add-back hormone therapy is possible. Furthermore, GnRHa are expensive and not readily available to women worldwide, especially in developing countries [3].

The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®)

Because GnRHa provoke hypoestrogenism and can lead to bone loss, new therapeutic options, including the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®), are being investigated [4]. The mechanism of action of the LNG-IUS on endometriosis is unknown but appears to differ from that of GnRHa, since the LNG-IUS neither inhibits ovulation in the majority of women nor provokes hypoestrogenism [5]; moreover, the concentration of levonorgestrel is high only inside the uterus [6]. Levonorgestrel is believed to act on endometriosis lesions by depleting the estrogen and progesterone receptors through inhibition of the synthesis and expression of estrogen receptors, resulting in an antiproliferative effect, glandular atrophy and decidualization. An increase in apoptosis and a reduction in Bcl-2 protein, an inhibitor of apoptosis in the endometrial stroma, have also been described. In addition, the effect of the LNG-IUS on pain control may occur through the reduction of local vascular angiogenesis, reduction in the congestion of pelvic vessels and an increase in apoptosis [7].

Although endometriosis is a frequent cause of infertility, not all patients with endometriosis wish to conceive and some contraceptive methods, including the LNG-IUS, have been used to control pain [4]. Previous studies have suggested that the LNG-IUS offers effective relief from chronic pelvic pain, dyspareunia and dysmenorrhea associated with endometriosis and adenomyosis, and improves the staging of endometriosis [7–10].

Efficacy studies

In two studies, Vercellini et al. [9, 10] evaluated the efficacy of the LNG-IUS in the treatment of recurrent dysmenorrhea in women following surgery for endometriosis. Both studies reported a drop in visual
analogue scale (VAS) pain measurements (1–100) from 76 to 34 after 12 months of use.

“The LNG-IUS neither inhibits ovulation in the majority of women nor provokes hypoestrogenism; moreover, the concentration of levonorgestrel is high only inside the uterus.”

Fedele et al. [8] evaluated the effectiveness of the LNG-IUS in controlling pain and lesion size in women with endometriosis of the rectovaginal septum. Dysmenorrhoea, pelvic pain and deep dyspareunia improved, and the size of the endometriotic lesions reduced significantly on ultrasonographic evaluation.

Lockhat et al. [11] evaluated the LNG-IUS over a 6-month period in 34 women with minimal to moderate endometriosis. Among the 29 women who completed the study, significant improvements were observed in the severity and frequency of pain and in the staging of the disease, with 68% of users opting to continue using the LNG-IUS beyond 6 months. Side effects were assessed and pelvic pain was evaluated using a VAS (1–10) in the same women after 3 years of LNG-IUS use [7]. The continuation rate at 36 months was 56%. Most of the discontinuations were due to unacceptable bleeding disturbances and persistent pain.

However, these studies were either non-comparative or in comparison with expectant management only. Our group conducted a study in which 82 women with endometriosis were randomly assigned to the LNG-IUS (n = 39) or to GnRHa (n = 43) [12]. All the patients presented with cyclic chronic pelvic pain with or without dysmenorrhoea and all had a VAS (1–10) pain score >3 during the pretreatment cycle. In the pretreatment month, the VAS pain score was 7.3 ± 0.3 (mean ± SEM) in both groups, while 17 women in each treatment group had initial VAS pain scores >3 and <7, and 22 and 26 women in the LNG-IUS and GnRHa groups, respectively, had VAS pain scores >7.

A significant reduction in pain score was observed by the end of the first treatment month and this therapeutic effect persisted throughout the 6 months of the study with no statistically significant differences between the two groups. Between baseline and visit 6, there was a six-point decrease in VAS pain score in both patient groups and no significant difference between the two groups (Figure 1). No relationship was found between the reduction in pain score at each month of observation and the VAS pain score observed at baseline in either treatment group. Moreover, women with stage III or IV endometriosis experienced a significantly faster improvement in VAS pain score in comparison with women with stage I or II of the disease.

Bleeding patterns were evaluated daily in all patients. Amenorrhoea occurred earlier in the group of GnRHa users, with 34% and 71% of patients reporting amenorrhoea by the second treatment month in the LNG-IUS and GnRHa groups, respectively. At the end of 6 months of observation, 70% and 98% of users of the LNG-IUS and GnRHa, respectively, were amenorrhoeic (Figure 2). Side effects of abdominal distension or peripheral oedema were similar in both treatments groups; however, more symptoms of breast tenderness were observed in LNG-IUS users. Although the pain score and menstrual bleeding reduced significantly in both treatment groups, there was no significant increase in the Psychological General Well-Being Index in either group at 6 months of follow-up.

Discussion

Due to the high prevalence of the disease there has been an increased demand for the treatment of endometriosis-related chronic pelvic pain, dysmenorrhoea and dyspareunia. In addition, although endometriosis is linked with infertility, many women wish to postpone pregnancy and others are diagnosed only after their family is already complete. For these women, therapeautic options must be found that offer pain relief, bleeding control and long-term treatment at an affordable cost and with minimal side effects.

GnRHa remain the gold standard treatment of endometriosis-associated chronic pelvic pain, mainly because they promote anovulation, hypoestrogenism with amenorrhoea, and a reduction in endometriotic lesions. However, the hypoestrogenism induced by the medication places limitations on its use, principally because of the need to restrict the duration of treatment, the risk of bone loss with consequent osteopenia or osteoporosis, and side effects such as mood changes and vaginal dryness [13]. Although the daily
dose of levonorgestrel in LNG-IUS users is low without peaks in plasma concentration, we cannot ignore the presence of side effects in these users, mainly ascribed to hormonal influence. The more commonly reported were acne, other skin problems, weight changes, nausea, headache, depression, other mood changes and breast tenderness [14]. The three side effects which more frequently accounted for discontinuation were depression, acne and headache; however, the discontinuation rates were low [15].

The LNG-IUS offers several advantages for the treatment of endometriosis and pain control. Although in our study, treatment was limited to 6 months, other studies have evaluated the device over a period of 12 months [11] and 3 years following insertion [7]. Since the LNG-IUS has been approved for 5 years of use, its therapeutic effect is potentially much longer lasting. However, no data on long-term use have been published.

Figure 2: Occurrence of amenorrhoea in each treatment group during 6 months of treatment.

The rate of release of levonorgestrel from the LNG-IUS is 20 µg/day during the first year, slowly decreasing throughout the 5 years of use [5]. Despite the small amount of levonorgestrel released by the device, amenorrhoea is achieved in approximately 60% of women after 6 months of use and this percentage is maintained throughout the duration of use. Therefore, based on the induced endometrial atrophy and amenorrhoea, it is possible to speculate that the LNG-IUS may be effective in controlling chronic pelvic pain for the same period of time. It is important to note that the longer the effect on pain control, the greater the cost-effectiveness of the LNG-IUS. Moreover, the market cost of the LNG-IUS in countries such as Brazil is only a little higher than the cost of one ampoule of GnRHa.

Amenorrhoea was established earlier in GnRHa users than in LNG-IUS users, and the LNG-IUS users experienced light, irregular bleeding during the initial months of use (although with pain control), similar to that observed in users of the device for contraception [16]. However, at 6 months of follow-up, 70% of the women were amenorrhoeic and would probably remain so throughout their use of the method. For women with endometriosis who need long-term treatment, the LNG-IUS may be the treatment of choice, since it permits the same system to be used for at least 5 years with no modifications in estrogen levels and consequently few side effects, while at the same time providing highly effective contraception. Its short-term efficacy was similar to that of GnRHa, but its long-term use requires further evaluation.

References

The levonorgestrel-releasing intrauterine system (Mirena®) in the peri- and postmenopause

David Sturdee

Department of Obstetrics and Gynaecology, Heart of England NHS Foundation Trust, Solihull Hospital, Solihull, UK

Introduction

Women in the perimenopausal years are amongst the most frequent attenders for gynaecological advice, and especially concerning menorrhagia or dysfunctional uterine bleeding. The gradual decline in the control of menstruation prior to the menopause, together with an increasing menstrual loss (Figure 1), can have a major impact on quality of life.

Unsatisfactory bleeding is also one of the commonest causes of dissatisfaction with hormone replacement therapy (HRT), which can often be resolved by using a regimen with continuous progestogen in addition to estrogen to keep the endometrium permanently suppressed. The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) is a most logical and satisfactory measure for resolving both these problems in peri- and postmenopausal women.

The perimenopause

Irregular dysfunctional uterine bleeding in the perimenopause can often be regulated by oral cyclical progestogen therapy, but regular and heavier periods do not respond well to this regimen and the intrauterine delivery of progestogen is usually more effective.

In a randomized comparative trial of women with menorrhagia treated with either the LNG-IUS or oral norethisterone 5 mg 8 hourly from days 5 to 26, there was a similar reduction in blood loss after 3 months, but the continuation rates were significantly different. In the LNG-IUS group 17 out of 22 (77%) wished to continue, whereas in the norethisterone group only 4 out of 18 (22%) continued with treatment, indicating a strong preference for the intrauterine treatment [1]. The combination of good control of the menstrual loss and reliable contraception means that the LNG-IUS is becoming increasingly popular for perimenopausal women for whom hysterectomy has for too long provided the only definitive relief from unwanted menstrual problems and pregnancy. The common clinical dilemma of the 45- to 50-year-old woman with distressing and restricting menorrhagia for whom the timing of the menopause is indeterminable, and yet the prospect of possibly an unnecessary hysterectomy is unsatisfactory, can often be resolved by the LNG-IUS.

In recent years there has been a welcome gradual reduction in the rates of hysterectomy just for dysfunctional uterine bleeding. This is partly due to wider education on the merits of more conservative managements such as oral tranexamic acid, endometrial ablation techniques and also the LNG-IUS. A long-term follow-up study of 50 women who were on the waiting list for hysterectomy because of menorrhagia reported that 67% managed to avoid hysterectomy by using the LNG-IUS [2]. This could have considerable health cost-savings if such a practice were adopted across large populations. More recent evidence was reported by Hurskainen and colleagues [3] from a randomized controlled trial of 236 women with menorrhagia at a mean age of 43 years. Participants were randomly assigned to treatment with either the LNG-IUS (n = 119) or hysterectomy (n = 117) and were monitored for 5 years. At the end of the study, the two groups did not differ significantly in terms of health-related quality of life (HRQOL) or psychosocial well-being. Although 42% (n = 50) of the LNG-IUS group eventually underwent hysterectomy,
the discounted direct and indirect costs in the LNG-IUS group at US $2817 (95% CI 2222–3530) per participant remained substantially lower than in the hysterectomy group at US $4660 (95% CI 4014–5180). Satisfaction with treatment was similar in both groups, but the conclusion was that by improving HRQOL at relatively low cost, the LNG-IUS offers a wider availability of choices for the patient and may decrease costs due to interventions involving surgery.

Transition to the postmenopause

Many women are using the LNG-IUS for contraception during the years prior to the menopause, but now that the device has been licensed in many countries also for use as the progestogen component of continuous combined HRT regimens, it can provide a convenient transition from contraception to HRT [4]. Traditionally women requiring HRT in the perimenopause are advised to use a sequential estrogen and progestogen regimen, which should give a regular and controlled withdrawal bleed. However, bleeding is one of the commonest reasons for dissatisfaction with HRT, and for longer term use and for better protection of the endometrium the continuous combined estrogen and progestogen therapy (CCEPT) regimens are advocated. Such regimens provide the same benefits of symptom relief as a sequential regimen but avoid cyclical bleeding. As with the use of the LNG-IUS for the control of menorrhagia, after the initial insertion it may take several months for the full effect on bleeding to be realized and women must be encouraged to persevere, but thereafter the bleeding is similar to that of other forms of CCEPT. Figure 2 shows the bleeding profile of women using the LNG-IUS together with a transdermal patch delivering 20 μg estradiol (n = 20) compared with oral estradiol valerate 2 mg combined with norethisterone acetate 1 mg daily (n = 20). For the initial 3 months there was more bleeding in the LNG-IUS group, but thereafter the bleeding was similar in the two groups [5]. In addition, use of sequential HRT regimens for over 5 years has been associated with an increased risk of endometrial carcinoma [6], whereas CCEPT does not increase the risk and may even provide added protection against endometrial carcinoma [7].

Further evidence on the endometrial suppressive effect of intrauterine progestogen comes from a study of 40 postmenopausal women using the LNG-IUS with oral or transdermal estradiol. Endometrial thickness decreased from 5 mm (range 0–14 mm) at baseline to 2.4 mm (range 0–3.6 mm) after 5 years. Of the women completing 5 years of therapy, 64% were totally amenorrhoeic [8]. A more recent randomized study of postmenopausal women taking oral estradiol valerate 2 mg daily and using either the LNG-IUS providing continuous progestogen or oral sequential medroxyprogesterone acetate showed a reduction in endometrial proliferation with the LNG-IUS and an increase in progestogen-induced atrophy (Table I). After 6 months, 54 (98%) of the 55 women had no bleeding.

Riphagen [10] reviewed the intrauterine application of progestogens in HRT and reported on 16 studies of LNG-IUS use in combination with different types and routes of estrogen in over 800 women. Durations of therapy ranged from 6 months to 5 years and in none of them was there any case of endometrial hyperplasia or carcinoma. He concluded that these data confirm the endometrial safety of this application. The apparent increased risk of breast cancer when progestogen is added to estrogen in HRT regimens as reported by the Women’s Health Initiative [11] and

| Table 1: Endometrial histology and thickness at 12 months with the LNG-IUS vs. sequential oral medroxyprogesterone acetate in postmenopausal women taking continuous estradiol valerate [9]. |
|-----------------------------------------------|-----------------|-----------------|
| No. of women experiencing atrophy            | 2 (4%)          | 3 (6%)          |
| No. of women experiencing proliferation      | 0               | 18 (38%)        |
| No. of women experiencing progestogen-induced atrophy | 53 (96%)        | 26 (55%)        |
| Endometrial thickness (mm)                    | 3.3             | 4.0             |
the Million Women Study [7] has raised concern about the relative merits of additional progestogen. These studies relate to oral and transdermal administration and with the LNG-IUS the circulating plasma levels of levonorgestrel are much lower than with oral or transdermal HRT regimens. Recent data from the Finnish Cancer Registry provide reassurance that LNG-IUS users have the same incidence of breast cancer as the general population [12].

Conclusions

— The LNG-IUS is especially suitable for the perimenopausal woman for the control of dysfunctional uterine bleeding.
— It can be continued through the menopausal transition after which estrogen therapy may be added by any route that is favoured to provide continuous combined HRT for the relief of menopausal symptoms.
— The LNG-IUS can also provide the most reliable contraception during the menopausal transition at a time when other methods may be less satisfactory.
— After insertion in the premenopausal woman or as part of an HRT regimen, there may be some initial irregular bleeding, but with perseverance this will usually resolve.

References


Endometrial effects of levonorgestrel intrauterine delivery

Takeshi Maruo

Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, Kobe, Japan

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) was originally developed as a contraceptive but has also been shown to be effective in achieving a significant reduction in menstrual blood loss [1, 2]. This non-contraceptive benefit of the LNG-IUS implies that it may be a safe, non-surgical alternative in the management of menorrhagia.

We observed that use of the LNG-IUS resulted in a striking reduction in menorrhagia in all women with adenomyosis and intramural myomas except for women with submucous myomas [3, 4]. Although some women with large intramural myomas had spontaneous expulsion of the device at various intervals, they nevertheless requested reinsertion because of the remarkable reduction in menorrhagia, which resulted in significant increases in haemoglobin levels (Figure 1). By contrast, in menorrhagic women with adenomyosis there were no spontaneous expulsions of the device during 3 years of use and significant increases in haemoglobin levels were recorded 3 months after insertion. Thus, the LNG-IUS has been proven to be an effective modality in the long-term management of menorrhagia due to adenomyosis and uterine myomas except for submucous myomas. These clinical experiences prompted us to characterize the effects of levonorgestrel on endometrial proliferation and apoptosis.
Effects of the LNG-IUS on the endometrium

The effects of the LNG-IUS on endometrial proliferation and apoptosis were evaluated by proliferating cell nuclear antigen (PCNA) expression, apoptosis, Fas and Bcl-2 protein expression in the endometrium, which were determined at the early proliferative phase of the menstrual cycle before and 3 months after insertion in menorrhagic women with adenomyosis [5].

PCNA, immunolocalized both in the nuclei of the endometrial glands and stroma, became less abundant 3 months after insertion (Figure 2). Determination of the mean percentages of PCNA-positive nuclei in the endometrial glands and endometrial stroma showed that the PCNA-positive rate, both in the endometrial glands and endometrial stroma, was significantly lower after 3 months of LNG-IUS use (p < 0.05).

Apoptotic nuclei assessed by the TUNEL method were noted on the endometrial surface and in the endometrial glands and stroma. The apoptotic nuclei in the endometrium seemed more abundant 3 months after insertion (Figure 2). Determination of the mean percentages of PCNA-positive nuclei in the endometrial glands and endometrial stroma showed that the apoptosis-positive rate in the nuclei of the endometrial glands and endometrial stroma obtained 3 months after insertion was significantly higher (p < 0.05).

Before LNG-IUS insertion, immunohistochemical staining of Fas antigen in the endometrium was scarcely apparent, being only slightly visible in the endometrial glands. The immunostaining intensity of Fas antigen became predominant in both the endometrial glands and stroma 3 months after insertion (Figure 4). On the other hand, Bcl-2 protein, immunolocalized in the cytoplasm of the endometrial glands but not in the stroma, became scanty 3 months after insertion. These results demonstrate that LNG-IUS use resulted in a decrease in endometrial proliferation and in an increase in apoptosis in endometrial glands and stroma.

Discussion

Levonorgestrel released locally from the LNG-IUS has been shown to inhibit the expression of both estrogen and progesterone receptors in the human endometrium [6]. This decrease in estrogen and progesterone receptors in the endometrium was suggested as a contributory mechanism to the amenorrhea associated with LNG-IUS use. By contrast, Pakarinen et al. [7] reported that the local release of levonorgestrel abolished cyclical changes in the endometrium in relation to the menstrual cycle and reduced endometrial thickness, as evidenced by ultrasonography. Levonorgestrel caused atrophy of the endometrial glands and deciduation of the stroma [8, 9]. Thinning of the mucosa was evident, and the stroma became swollen during LNG-IUS use. Based on the remarkable reduction in PCNA-positive cells in the endometrium during LNG-IUS use, it is now evident that insertion results in a significant decrease in the proliferative activity of endometrial glands in menorrhagic women with adenomyosis.

The role of apoptosis in the endometrium in menstrual cycle regulation has been reported. Apoptosis was detected in the early proliferative phase, mainly in the glandular epithelium with few positive cells in the stroma, but decreased during the secretory phase of the menstrual cycle [10]. In our study [5], although minimal apoptosis was detected in the endometrial samples taken in the early proliferative phase before LNG-IUS insertion, there was a significant increase in apoptosis-positive nuclei in the endometrium 3 months after LNG-IUS insertion. In accordance with the increased apoptosis in the endometrium, Fas expression in the endometrium became prominent 3 months after insertion, not only in the glandular cells but also in the stromal cells. This finding was of significant interest in understanding the molecular basis of the increased apoptosis that occurs in the endometrium during LNG-IUS use. Consistent with this observation, minimal Bcl-2 protein expression was detected in the endometrial curettage samples obtained during the early proliferative phase before insertion, which became less detectable 3 months after insertion [10]. Decreased Bcl-2 protein expression in the endometrium after 3 months of LNG-IUS use may also be linked to the increased apoptosis that occurs in the endometrium during LNG-IUS use. Although no differences in the levels of expression of Bcl-2, Fas and caspase-3 in the endometrium were noted between levonorgestrel implant (Norplant®) users with and without breakthrough bleeding [11], the lack of effect of levonorgestrel on the endometrium in Norplant® users might be due to much lower concentrations of levonorgestrel in the endometrial tissues compared with those in LNG-IUS users.

The current study demonstrates a decline in proliferative activity, associated with an increase in apoptosis, in the endometrial glands and stroma after LNG-IUS insertion. The increased apoptosis in the endometrium after 3 months of LNG-IUS use was congruent with a remarkable increase in Fas antigen expression, together with a decline in Bcl-2 protein expression in the endometrium. As Fas antigen is a mediator of apoptosis, and Bcl-2 protein is an apopto-
sis-inhibiting gene product, the increased apoptosis in the endometrial glands and stroma that occurs during LNG-IUS use may represent an underlying molecular mechanism that causes atrophic changes of the endometrium, leading in turn to the remarkable improvement of menorrhagia. This may explain the molecular basis of the beneficial effect of LNG-IUS on menorrhagia.

Figure 2: Immunohistochemical localization of PCNA before (2A) and 3 months after (2B) LNG-IUS insertion. PCNA expression in the endometrium appeared less abundant 3 months after insertion. E, Endometrial gland epithelium; S, endometrial stroma. Scale bar = 10 μm.

Figure 3: Apoptosis as assessed by TUNEL method before (3A) and 3 months after (3B) LNG-IUS insertion. The apoptosis-positive nuclei in the endometrium appeared more abundant 3 months after insertion. E, Endometrial gland epithelium; S, endometrial stroma. Scale bar = 10 μm.

Figure 4: Immunohistochemical localization of Fas antigen in the endometrium before (4A) and 3 months after (4B) LNG-IUS insertion. Fas antigen expression became more abundant in both the endometrial glands and stroma 3 months after LNG-IUS insertion. E, Endometrial gland epithelium; S, endometrial stroma. Scale bar = 10 μm.
Future options for the intrauterine delivery of progestogens in the prevention of gynaecological disease

Ian S. Fraser

Department of Obstetrics and Gynaecology, University of Sydney, Sydney, NSW, Australia (helena@med.usyd.edu.au)

Introduction

Progestogen delivery into the uterine cavity for the purposes of developing a new contraceptive approach began in the late 1960s with the design of the Progestasert®. This contraceptive system released progesterone at a relatively constant rate over a period of about 1 year, and it soon became obvious that it greatly reduced the overall heaviness of menstrual bleeding, although troublesome but light breakthrough bleeding was an issue [1].

The potential of this approach for contraception was rapidly realized, and Professor Tapani Luukkainen and the Population Council soon began to develop an intrauterine system releasing levonorgestrel (LNG-IUS; Levonova® and Mirena®) [2]. This system exhibited a dramatic impact in reducing the heaviness of menstruation in women whose bleeding was excessive [3]. This sequence of observations was the beginning of the realization that the intrauterine delivery of progestogens could have major therapeutic benefit for certain established gynaecological symptoms or disease. More recent experience has amply confirmed the potential value of the LNG-IUS for treating a range of conditions and it is hoped that the LNG-IUS and similar systems [4] may even play a valuable role in the prevention of symptoms and disease.

Gynaecology has traditionally been a surgical specialty, but the introduction of intrauterine progestogen delivery systems has so rapidly built on the early promise of the combined oral contraceptive pill as a medical gynaecological therapy [5] that surgery is rapidly becoming a much less prominent part of the specialty of gynaecology in many parts of the world.

Intrauterine progestogens in established gynaecological conditions

The articles in this issue highlight evidence for the use of progestogen-releasing intrauterine systems for the active treatment of several gynaecological conditions. Evidence supporting use of the LNG-IUS for treatment of excessively heavy menstrual periods is substantial [6]. This benefit may extend to heavy periods due to ovulatory and anovulatory dysfunctional uterine bleeding, endometrial hyperplasia, disorders of haemostasis, uterine fibroids, endometrial polyps, endometriosis and adenomyosis. The LNG-IUS may also have benefits in treating symptoms of primary
Intrauterine progestogens in the prevention of gynaecological disease and symptoms

A logical extension to the concept of using the LNG-IUS for the active treatment of gynaecological conditions is to use its long-acting properties to prevent progression of symptoms or disease, to prevent recurrence after surgery and to prevent the onset of symptoms in those at risk (Table I). Unfortunately, evidence currently available to support the use of progestogen delivery systems for these preventive indications is limited, but the promise is substantial.

Anecdote, case reports and extrapolation from therapeutic studies indicate the need for well-designed clinical studies, preferably comparative and randomized, to prove the concepts of ‘prevention’ for specific symptoms and conditions. This approach has the potential to herald a new era of medical management in gynaecology and to provide partial ‘protection’ against the adverse effects of a ‘modern’ lifestyle (such as the gynaecological consequences of obesity, delayed childbearing and regular repeated menstrual cycles over many years) [10].

Prevention of heavy menstrual bleeding
The LNG-IUS is proving to be such an effective therapy for heavy menstrual bleeding that it seems highly probable that it can be used as an effective preventive therapy for many women identified as being at risk of developing heavy menstrual bleeding. The key question here is to identify those women who are at risk (e.g. young women with a family history of disorders of haemostasis, polycystic ovary syndrome, women in the menopause transition, with a history of uterine fibroids, etc). Some of these women will be nulliparous and adolescent; however, there is substantial clinical experience to indicate that the LNG-IUS will be effective in the majority of young women, although the insertion procedure may be more difficult than in parous women. The development of a ‘slimline’ device releasing levonorgestrel 10 μg/24 h would be very valuable in these young women [11].

Prevention of endometriosis and its recurrence
There is increasing evidence to suggest that endometriosis is primarily an endometrial disease, and that suppression of endometrial proliferation with the LNG-IUS may prevent recurrences of endometriosis following laparoscopic excision [12]. Hence, the device may also be valuable in preventing the onset of endometriosis in young women with a strong family history of the disease. This needs to be formally tested.

Prevention of growth and recurrence of uterine fibroids
Several investigations have suggested that uterine fibroids may show a decrease in size or may increase in size more slowly than expected following LNG-IUS insertion. This may be of benefit in reducing pressure symptoms and heavy bleeding as well as avoiding surgical management. There are also data from one large-scale randomized 5-year comparative trial which showed substantially lower detection and surgery rates for uterine fibroids in LNG-IUS users [15].

Prevention of fertility
Case-control data suggest that complaint of infertility is significantly less common in women who have used the combined pill for some years [16]. Suggestive data also support the expectation that the LNG-IUS may protect against future complaint of infertility, possibly through minimization of the consequences of endometriosis, fibroids and acute episodes of pelvic infection.

Avoidance of hysterectomy
Clear evidence has begun to emerge to illustrate a major reduction in rates of hysterectomy for heavy bleeding

**Table I: Indications for use of the LNG-IUS for possible prevention of gynaecological symptoms and disease.**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Potential underlying cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy menstrual bleeding</td>
<td>Previous ovulatory or anovulatory dysfunctional uterine bleeding</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td></td>
<td>Intramural or subserous fibroids</td>
</tr>
<tr>
<td></td>
<td>Adenomyosis and endometriosis</td>
</tr>
<tr>
<td></td>
<td>Disorders of haemostasis</td>
</tr>
<tr>
<td></td>
<td>Menopause transition</td>
</tr>
<tr>
<td>Irregular menstrual bleeding</td>
<td>Previous endometrial polyps</td>
</tr>
<tr>
<td></td>
<td>Previous endometrial hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>Primary dysmenorrhoea</td>
</tr>
<tr>
<td></td>
<td>Recurrent endometriosis</td>
</tr>
<tr>
<td></td>
<td>Adenomyosis</td>
</tr>
<tr>
<td></td>
<td>Acute episodes of pelvic infection</td>
</tr>
<tr>
<td>Infertility</td>
<td>Endometriosis</td>
</tr>
<tr>
<td></td>
<td>Acute episodes of pelvic infection</td>
</tr>
<tr>
<td></td>
<td>Uterine fibroids</td>
</tr>
</tbody>
</table>

© 2006 Medical Forum International
menstrual bleeding and for benign gynaecological disease (Figure 1) [17, 18]. These reductions correlate inversely with increased use of the LNG-IUS, whereas endometrial ablation has probably played little role.

Conclusions

The evidence suggests that preventive effects of the LNG-IUS (and possibly other related systems) against development of a range of gynaecological symptoms and diseases will continue to reduce the need for major surgery in the future. This increase in appreciation of the therapeutic value of intrauterine delivery of progestogens will undoubtedly be extended further to primary and secondary prevention applications. The time is ripe for design of formal studies to prove these concepts. Future research will also be directed towards intrauterine delivery of other promising therapeutic agents (such as progesterone receptor modulators).

References