The benefits and risks of using a levonorgestrel-releasing intrauterine system for contraception

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Abstract

The contraceptive profile of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®) is well established, with efficacy similar to that achieved with sterilization and rapid return to fertility after discontinuation of use. The LNG-IUS is typically associated with transient menstrual disturbance during the first few months of use, but this usually settles with continued use, with a concomitant decrease in menstrual blood loss. Overall, the safety profile of the LNG-IUS has been well established across a wide population of women, and the available data do not suggest that the LNG-IUS adversely affects bone health or increase the risk of adverse cardiovascular events or breast and uterine cancers. This article reviews the literature to provide updated information on the risks and benefits associated with the LNG-IUS, particularly focusing on its use in contraception.

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1. Introduction

Intrauterine devices (IUDs) have been used as a method of contraception for over 2000 years [1], but their use became more commonplace in the second half of the 20th century. The larger inert plastic IUDs of the early 1960s were quickly replaced by the smaller, copper-bearing, ‘T’-shaped devices of the 1970s in the hope that associated dysmenorrhea and heavy menstrual bleeding would be less [2]. The first medicated IUD releasing progesterone, Progestasert, was introduced in 1976 but never gained wide popularity because of its short, 1-year life span. In the late 1970s, Dr. Tapani Luukainen began work on designing and then conducting trials of a plastic ‘T’-shaped IUD releasing the synthetic progestin levonorgestrel (LNG) — the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®). It was first approved for contraceptive use in Finland in 1990 and is now recognized as one of the most effective methods of contraception with a number of additional health benefits including reduction in heavy menstrual blood loss and endometrial protection during estrogen replacement therapy.

This article reviews the literature to provide updated information on the risks and benefits associated with the LNG-IUS particularly focusing on its use in contraception.

2. Methodology

Relevant articles were identified using the Ovid interface to search both PubMed and Embase simultaneously up to 31 March 2011. Key search terms included Mirena, levonorgestrel-releasing, LNG-IUS, or LNG-IUD combined with contraception or contraceptive. This risk–benefit review of the LNG-IUS was performed with the aim of overviewing the most up-to-date information (focusing on articles published from 2004 to 2011 where appropriate data are available) regarding the use of the LNG-IUS in contraception.

Conflicts of interest: Dr Mansour has received support to undertake research, attend clinical meetings and scientific advisory boards for Bayer Pharma AG.

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3. Clinical overview

3.1. Mechanism of contraceptive action

Details of the LNG-IUS design, pharmacokinetic data, and mode of action can be found in previous summary publications [3,4]. Briefly, LNG is released directly into the endometrial cavity at an initial rate of 20 mcg/day declining towards 10 mcg/day by the end of 5 years. The maximum systemic LNG levels are reached shortly after insertion, remain fairly stable during the first weeks and decline with time thereafter [3]. Mean systemic serum LNG levels in women of reproductive age appear to range between 100 and 200 pg/mL during 6 years of LNG-IUS use [4]. However, individual systemic LNG levels are subject to wide variations, and systemic LNG levels >200 pg/mL have been reported in women with HIV or endometriosis during the first 12 months [5,6]. In addition, both body weight/body mass index and sex hormone-binding globulin have been shown to affect systemic LNG levels — lower systemic LNG levels with increased body mass index/weight [7,8] or lower sex hormone-binding globulin levels [4,9].

The contraceptive effects of the LNG-IUS are mediated mainly by the action of the high concentration of LNG within the endometrium (LNG levels in the myometrium and in the fallopian tubes are significantly lower than in the endometrium), causing changes in cervical mucus that act as a barrier to sperm penetration [10], and endometrial atrophy [11–14], as well as expression of glycodelin A within the uterine glands that inhibit sperm–egg binding [15], thus preventing fertilization and/or implantation. A foreign-body reaction is also observed [14,16].

Although some women experience ovulation suppression during the first year of using the LNG-IUS [4,17,18], most cycles are ovulatory. There is no reduction in serum estradiol (E2) levels with LNG-IUS use — E2 levels remain within the range of a ‘normal’ menstrual cycle [4]. Prevention of endometrial growth with the use of the LNG-IUS leads to a decrease in menstrual blood loss; however, menstrual bleeding does not itself reflect ovarian function [17]. Average LNG levels are similar in women with amenorrhea as those with regular menstrual bleeding, in addition to similar E2 and progesterone levels and the incidence of ovulation [17].

3.2. Contraceptive profile

The contraceptive profile of the LNG-IUS is well established, with efficacy approaching that achieved with female sterilization — a pregnancy rate of 0.2% is observed during the first 12 months of typical use [19]. Contraceptive efficacy is not affected by poor compliance or age, and the cumulative gross failure rates at 5 years per 100 users range between 0.5 and 1.1 in prospective clinical studies and routine clinical practice [20–23].

Long-term use of the LNG-IUS immediately following a first-trimester abortion has been shown to have a gross failure rate of 0.8 at 5 years that was significantly (p<.001) lower than the corresponding rate of 9.5 with a 200-mm² surface area copper IUD (Nova T 200) [24]. Moreover, the use of the LNG-IUS or copper IUDs after an abortion has been shown to significantly reduce the risk of repeat abortions compared to the use of other contraceptive methods [25–27]. Similarly, a decision analysis model showed that women with an IUD inserted immediately after an abortion were expected to have fewer unplanned pregnancies and repeat abortions than women scheduled for fitting of an IUD at a subsequent follow-up visit [28]. This was later confirmed by a randomized trial comparing immediate IUD placement (either the LNG-IUS or a copper IUD within 15 min) following uterine aspiration for induced or spontaneous abortion versus delayed placement (2–6 weeks later), where all the women randomized to receive immediate IUD placement (n=258) received their chosen IUD, whereas only 71% (226/317) randomized to the delayed group returned for their IUD placement visit [29]. Subsequently, during 6-month follow-up, there were five pregnancies in the delay-placement group in women who never received an IUD compared with none in the immediate-placement group. Failure to return for placement was also the most common reason (69%; 60/87) for nonplacement of an IUD in women who planned to have an IUD at their postoperative visit following an elective abortion in a retrospective chart review of US patients [30]. Additionally, uptake of long-acting reversible contraceptives including the LNG-IUS by women postabortion may be increased by eliminating costs and raising awareness about the benefits of these methods among clinicians and patients [31].

The continuation rates for LNG-IUS use are typically ≥76% at 1 year, decreasing to between 33% and 53% at year 5 in contraceptive clinical studies [21,22,32–34]. Higher continuation rates have been observed in routine clinical practice [35,36]. A large Finnish postmarket survey reported continuation rates of 93% at 1 year, decreasing to 65% by 5 years [35]. In addition, data from the General Practice Research Database (GPRD) obtained between 1997 and 2002 suggest 1-year continuation rates of 98%, decreasing to 85% at 5 years [36]. However, the UK Family Planning and Reproductive Health Research Network-conducted study between 1992 and 1995 reported lower net continuations rates of 70% and 40% at 1 and 5 years, respectively [20]. The difference in the continuation rates between the GPRD and UK Family Planning and Reproductive Health Research Network continuation rates may be explained, in part, by when the studies were performed. The latter study was undertaken shortly after the LNG-IUS was first made available in the UK when physicians would have been less familiar with the system and identifying the most suitable women. Indeed, in the Finnish postmarket survey, the risk of premature removal of the LNG IUS was shown to be highest in women who experienced excessive bleeding [risk ratio 2.77; 95% confidence interval (CI) 2.51–3.07] and spotting.
(risk ratio 1.89; 95% CI 1.75–2.05) [35]. Giving LNG-IUS product profile information to patients before insertion, particularly the possibility of occasional missed periods, was shown to be associated with high user satisfaction [37]. Along these lines, the authors of the UK Family Planning and Reproductive Health Research Network study acknowledged that counseling women about bleeding problems in the first few months after insertion, and the possibility of oligomenorrhea or amenorrhea, may improve continuation rates with the LNG-IUS [20].

An essential feature of any highly effective reversible method of contraception is that it should not adversely affect future fertility, which can be an important concern for some women [38]. Following removal of the LNG-IUS in women wanting to conceive, 1-year pregnancy rates typically range between 79% and 96% in prospective studies [39–41]. These findings are consistent with the 1-year pregnancy rate (92%) achieved in otherwise fertile women who proactively used ‘natural family planning’ to conceive [42].

3.3. Noncontraceptive health benefits of the LNG-IUS

In addition to its contraceptive effects, the LNG-IUS has a number of noncontraceptive health benefits that include treatment of heavy menstrual bleeding, reduction in symptoms associated with endometriosis and adenomyosis, alleviation of dysmenorrhea and endometrial protection during postmenopausal estrogen replacement therapy [43–47]. These benefits are mainly achieved by the constant release of LNG directly into the uterine cavity causing endometrial suppression. A comprehensive review of the additional noncontraceptive benefits of the LNG-IUS is beyond the scope of the current paper.

3.4. Safety and tolerability

During the first few months after placement of the LNG-IUS, women may experience transient hormonal side effects related to initial exposure to LNG, including nausea, depression, headache, breast tenderness and acne or other skin problems [21]. However, the rate of these subjective side effects decreases over time, which may be related to the gradual decline in LNG release rate from 20 mcg/day initially to 10 mcg/day towards the end of 5 years. The incidence of abdominal and back pain was reported to be higher after LNG-IUS insertion compared with oral contraceptives in young nulliparous women at 12 months (54.7% vs. 40.0%) [48].

Initial use of the LNG-IUS for contraception is typically associated with transient menstrual disturbance during the first few months of use, but this usually settles with continued use, with a concomitant decrease in menstrual blood loss (Fig. 1). During the first few months (first 90-day reference period) after insertion of the LNG-IUS, frequent or prolonged bleeding may be experienced by up to 35% of LNG-IUS users, decreasing to 4% by reference period 4 [49]. In addition, irregular bleeding occurs in about two thirds of women during reference period 1, decreasing to about one fifth in reference period 4. In contrast, up to 11% of women may experience amenorrhea or infrequent bleeding during the first reference period, increasing to 73% in reference period 4. Although amenorrhea may be considered a positive change by some women [50], it is a common reason for discontinuing use of the LNG-IUS [20], with 5-year cumulative gross discontinuation rates of 6%–20% per 100 users. Adequate counseling prior to insertion about the bleeding changes improves satisfaction with the LNG-IUS [37] and may increase continuation rates.

The LNG-IUS is effective for 5 years, after which it has to be replaced. In women who opted to replace the LNG-IUS after 5 years in an international, prospective, multicenter study, a slight increase in bleeding/spotting was seen with insertion of a new LNG-IUS, followed by a marked decrease in bleeding/spotting during the first year of use of the second LNG-IUS compared with the last 90-day reference period of the previous one [51] (Fig. 2). The median number of bleeding/spotting days in the last 90-day reference period of the first LNG-IUS was 7 days, which increased after insertion of the second LNG-IUS to 8 days, for the first 90-day reference period and then decreased to 4 days during the second to fourth reference periods. Importantly, the increased transient menstrual disturbance typically seen during the first few months (except for limited bleeding/spotting associated with the placement procedure) with the first LNG-IUS does not reoccur if the LNG-IUS is replaced immediately. Moreover, the patterns of bleeding observed with the first LNG-IUS predicts the patterns of bleeding with the second LNG-IUS [52]. For example, women with fibroids and those with any bleeding or prolonged spotting episodes at baseline continued to experience more bleeding/spotting than other women with the second LNG-IUS.

Continuing with the LNG-IUS from contraception to part of hormone replacement therapy does not appear to
adversely affect the bleeding profile. An open, multicenter, noncomparative study of 168 women transitioning into the menopause while using the LNG-IUS for contraception showed that the mean number of bleeding/spotting days between the last contraceptive 90-day reference and the first 90-day reference period of the hormone replacement therapy phase remained relatively stable at about 10 days [53]. However, a subsequent further reduction in the mean number of bleeding/spotting days (to 6 days) was observed through to the fourth 90-day reference period of the hormone replacement phase. It was also found that continuing with the LNG-IUS from contraception to part of hormone replacement had a positive effect on quality of life.

### 3.4.1. Insertion- and removal-related issues

Insertion of the LNG-IUS should be done by a skilled clinician, and efforts should be made to minimize patient discomfort. A postmarketing study monitoring insertion-related issues with the LNG-IUS (n=3519) compared with the Multiload copper 375 (n=17,468) in New Zealand reported difficulties with LNG-IUS insertion in 3.6% of women compared with 1.4% with the Multiload Cu 375 [54]. Although nulliparity is not a contraindication for LNG-IUS use, nulliparous women were reported to have 1.6-fold higher relative risk for difficult insertions compared with parous women; the corresponding relative risk for difficult insertions in nulliparous women relative to parous women with the Multiload Cu 375 was 1.9-fold higher.

In a recent noninterventional study of nulliparous women (n=224) attending family planning services for LNG-IUS insertion, there were six (2.7%) insertion failures [55]. The insertion was rated as easy by the majority (72%) of the inserters, most of whom were midwives. The procedure was considered painless by 19 (9%) women, moderately painful by 162 (72%) women and severely painful by 39 (17%) women. Of the women who attended a postinsertion follow-up at 12–16 weeks, 76% (165/216) were satisfied with their method, and interestingly, women in the youngest age group were more satisfied than those in the oldest age group (75% and 59%, respectively) [55].

In another study of predominantly parous women who chose to continue to use a second LNG-IUS (n=115; 76% of whom used it for contraception), insertion was rated as easy in 100 (87%) women [51]. Cervical dilation was used in eight (7%) women, and analgesics were given to 11 (10%) women before the procedure. No pain was reported during the insertion procedure in 23 women (20%), but mild-to-moderate and severe pain was reported by 84 (73%) and 8 (7%) women, respectively. Removal of the initial LNG-IUS was rated as easy in 97% of cases, and pain on removal was rated as mild-to-moderate and severe in 42% and 2% of women, respectively.

Although cervical priming with vaginal or sublingual misoprostol may facilitate LNG-IUS or copper IUD insertion in some groups of women (i.e., those with a narrow cervical canal including those with cervical stenosis or young, nulliparous women) [56], it does not appear to help ease the placement of the LNG-IUS in women with a previous successful LNG-IUS insertion [57]. In a 15-month prospective study, of which a subset of women participated in double-blind, randomized, placebo-controlled trial assessing sublingual misoprostol on the ease of placement of a subsequent LNG-IUS, there was no difference in the proportions of insertions judged as easy in women randomized to receive misoprostol (93%; 40/43) and placebo (91%; 42/46; p=1.0) [57]. No or mild pain at insertion was reported by 37% and 35% of women in the misoprostol and placebo groups, respectively, and severe pain was reported in 23% and 11% of women, respectively. However, adverse events related to the study drug were more common in the misoprostol group.

In a large, multicenter, open-label, uncontrolled, Phase IIIb study with investigators with no prior experience with the LNG-IUS, of the 509 women enrolled to receive the LNG-IUS, 96% (488) did so at the first placement attempt [58]. Of all the LNG-IUS insertions undertaken, 92% (467) were rated as easy by the investigators. About half (261, 51%) of the women received premedication with analgesics, cervical dilatation was performed in 33 (6%) women, and paracervical block was used in 88 (17%) women. Overall, mild pain or no pain during the procedure was reported by 347 (68%) women, 133 (26%) experienced moderate pain, and a further 29 (6%) experienced severe pain.
3.4.2. Uterine perforation

Uterine perforation is a rare but potentially serious complication associated with insertion of all IUDs. However, uterine perforations can be asymptomatic and may go undetected for some time. An analysis of 701 perforation cases from four national pharmacovigilance centers across the Netherlands, New Zealand, Switzerland and Germany found that among those cases with time to detection reported (n=559), the mean time to detection was 306 days. Perforation was suspected or discovered at the time of insertion in only 47 (8.4%) cases [59]. Severe pelvic pain during insertion and heavy bleeding may be indicative of uterine perforation with IUDs [59–61]. In this clinical setting, confirmation of correct placement by ultrasonography or X-ray is recommended.

Interim results from 31,844 women in the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD), a large, controlled, prospective study in six European countries, reported the incidence of uterine perforations as 0.53 per 1000 insertions with the LNG-IUS compared with 0.44 per 1000 insertions for two copper-IUDs [62]. This was consistent with the findings of an earlier postmarket study in New Zealand that reported the incidence of uterine perforations with the LNG-IUS as 0.06% and that with the Multiload Cu 375 as 0.03% [54].

As observed with copper IUDs, the risk of perforation with the LNG-IUS may be increased during lactation and the postpartum period [63,64].

3.4.3. Expulsions

With placement of an IUD, the risk of expulsion is approximately one in 20 women and is most common in the first 3 months after insertion [65]. However, a retrospective cohort study comparing the dislocation rate of the LNG-IUS with that of the Multiload Cu 375 (107 women with each intrauterine contraceptive) suggested that partial or complete expulsions were less likely to occur with the LNG-IUS [66]. In addition, there appears to be no association between the length of the endometrial cavity and risk of expulsion [67].

Expulsion rates with the LNG-IUS appear to be comparable between nulliparous and parous women, unlike copper IUDs where expulsion rates may be slightly increased in nulliparous women compared to those who are parous [68]. The onset of unacceptable bleeding after prolonged use of the LNG-IUS may indicate possible displacement of the system [69].

Pregnancies can occasionally occur due to unnoticed partial or complete expulsion of the device [21], and women should be advised to regularly check for the presence of the threads. ‘Missing’ threads can occur as a result of expulsion, the threads being drawn up into the uterus or cervical canal, uterine perforation or pregnancy [70]. When the device cannot be located within the uterine cavity, ultrasound followed by abdominal X-ray is the investigation of choice. If the LNG-IUS is located in the uterine cavity and removal is desired, then it can then be removed using long slender ‘alligator’-style forceps, utilizing ultrasound guidance if needed. Even if the LNG-IUS is not fundally placed within the uterine cavity, it should still continue to function as an effective contraceptive as even intracervical placement of an LNG-releasing device has prevented pregnancies [71,72].

Multicenter studies comparing the contraceptive reliability of the LNG-IUS and a copper IUD suggest that the majority of all expulsions occur in the first year and decline thereafter year-on-year [21,22,73–75]. Interim data from EURAS-IUD suggest expulsion rates of just 0.8% with the LNG-IUS and 1.4% with copper IUDs within the first year after insertion [62]. Many of those taking part in the EURAS-IUD are experienced IUD fitters, and this may help explain the lower expulsion rate.

Immediate (within 10 min of placental delivery) or delayed (10 min up to 72 h) postpartum placement is associated with increased copper IUD expulsion (both partial and complete) rates compared with interval (≥6 weeks postpartum) placement [76]. Although not supported by the product label, immediate (within 10 min) or early (10 min to 48 h) postpartum placement of the LNG-IUS was assessed in two small studies and shown to be a feasible option [77,78]: there were two expulsions (2/19; 10.5%) by 10 weeks postpartum in one study [77] and eight expulsions (8/30; 27%) up to 6 months postpartum in the second study [78]. In the latter study, no expulsions were reported following interval (≥6 weeks postpartum) placements (0/16). Lower expulsion rates were reported with IUDs (including the LNG-IUS) placed at the time of first-trimester medical abortion, with only four expulsions (4/97; 4.1%) during 3 months of prospective follow-up [79]. In a randomized study comparing placement of IUDs, including the LNG-IUS, immediately (within 15 min) following uterine aspiration for induced or spontaneous abortion versus delayed placement (2–6 weeks later), there were 11 (11/199; 5.5%) and 6 (6/178; 3.4%) partial and complete (partial defined as the presence of the IUD within the cervical canal, and complete as the passage of the IUD out of the cervix entirely) LNG-IUS expulsions by 6 months in the two groups, respectively [29]. In the latter study, there were eight (8/258; 3.1%) and five (5/226; 2.2%) partial IUD (LNG-IUS and copper IUD) expulsions in the immediate and delayed IUD placement groups, respectively, and five (5/258; 1.9%) and one (1/226; 0.4%) complete expulsions.

3.4.4. Pelvic infection

There may be a small increased risk of developing upper genital tract infections in the first month after insertion of an IUD, linked to the placement procedure as a result of the mechanical transfer of bacteria from the vaginal to uterus [80,81]. The risk of developing pelvic inflammatory disease is less than 1 in 100 in women who are at a low risk of sexually transmitted infections [65]. The risk of pelvic inflammatory disease has been reported to be lower with the LNG-IUS compared with a copper IUD [21,82]: gross
removal rates because of pelvic inflammatory disease were 0.5 and 2.0 per 100 women at 3 years (p=0.013) for the LNG-IUS and copper IUD, respectively, and 0.8 and 2.2 per 100 women (p<0.05), respectively, at 5 years. In a large Phase III study of the LNG-IUS (n=678), the gross cumulative rates per 100 users for pelvic inflammatory disease at 12, 24 and 60 months were 0.9, 1.2 and 1.2, respectively [20]. Prior to insertion of the LNG-IUS, the possibility of a sexually transmitted infection should be excluded. Carriers of gonorrhea or chlamydia are at an increased risk of pelvic inflammatory disease [81], as are women who have multiple sexual partners. Screening for chlamydia at the time of IUD placement and then treating the infection as appropriate following placement appear to be reasonable options [83]. However, routine screening for sexually transmitted diseases should be dependent on regional prevalence of these infections. There is no evidence to support routine screening for sexually transmitted infections before IUD insertion in women at low risk of such infections [80].

A retrospective cohort analysis of 286 women who had cervical cytology taken before and 1 to 2 years after fitting of an LNG-IUS failed to show a significant increased rate in any bacterial abnormalities and Candida colonization in the vaginal microflora [84]. However, first-time users of the LNG-IUS had increased combined odds of colonization or infection with Candida, bacterial vaginosis and/or aerobic vaginosis. It was not clear why first-time LNG-IUS users had an increased risk of any colonization or infection with these microbes, and these data need to be confirmed in prospective studies. Another study of 172 women assessing for symptoms and abnormal vaginal flora before and after fitting of either a copper IUD or the LNG-IUS showed that significantly more women developed abnormal vaginal discharge 4–6 weeks after insertion of a copper IUD than the LNG-IUS (27% vs. 14%, p=0.04) [85]. However, this trend was not significant by 6 months postinsertion. A long-term study of cervical smear samples from 187 LNG-IUS users over a 7-year period showed that the LNG-IUS had no significant effect on cytopathological abnormalities or other microbiological alterations following its placement, although an increase in the frequency of candidiasis was found from the fourth to the seventh year of use relative to the first year of use [86].

3.4.5. Functional ovarian cysts

As with other progestin-only contraceptives, functional ovarian cysts may occur with the LNG-IUS [87] and can be diagnosed when >2.5 cm in diameter (i.e., when larger than normal follicles) [88]. About 10%–12% of women using the LNG-IUS are diagnosed with functional ovarian cysts [70]. In the majority of women, the enlarged follicles are asymptomatic and disappear spontaneously within the first few months following diagnosis. In a large Phase III study of the LNG-IUS, 15 (2.5%) women developed ovarian cysts with another two suspected cases from 678 women over 5 years [20]. Another study reported that six (12%) women developed ovarian cysts (3–7 cm) up to 12 months after LNG-IUS insertion [87].

3.4.6. Pregnancies with the LNG-IUS in situ

In the large Finnish postmarket survey, of the 132 pregnancies originally reported in over 58,600 women-years of total exposure, 64 pregnancies occurred with the LNG-IUS in situ, and of these, 33 (52%) were ectopic [23]. The corresponding rates for ectopic pregnancy at 1 and 5 years per 100 users were 0.045 and 0.22, respectively. The risk of ectopic pregnancy with the LNG-IUS in clinical studies appears lower than with copper IUDs with 200 mm² surface area (0.02 vs. 0.25 per 100 women-years of exposure) [21], but similar to those reported with copper IUDs with >350 mm² surface area (0.02 per 100 women-years of exposure) [65]. In comparison, an estimated 1.4 per 100 pregnancies are likely to be ectopic in women using no contraception [65]. Removal of the LNG-IUS is recommended in women who become pregnant with the LNG-IUS in situ and who wish to continue their pregnancy. As the risk of ectopic pregnancy is high in this setting, women found to be pregnant with the LNG-IUS in place should also be followed closely for possible ectopic pregnancy until the possibility of this condition is excluded. Early removal is thought to decrease the associated increased risk of abortion and preterm labor, as is the case with copper IUDs [89].

3.4.7. Effect on breastfeeding

Current labeling guidance recommends that postpartum LNG-IUS placements be delayed for a minimum of 6 weeks after delivery or until the uterus has fully involuted. A small amount of the LNG dose is excreted into breast milk and, therefore, may reach the nursing infant [90]. However, a prospective, randomized, controlled trial assessing the effects of postpartum LNG-IUS use showed that it did not negatively influence breastfeeding or the growth and development of nursing infants compared with postpartum copper IUD use [91]. Although the World Health Organization recommends that the LNG-IUS should not be used during the first 4 weeks postpartum in those breastfeeding because of a possible risk to the neonate of steroid exposure [92], the US Centers for Disease Control and Prevention suggest that the method could be used even following immediate postpartum placement as the advantages of using the method generally outweigh the theoretical or proven risks [93].

3.4.8. Bone mineral density

Sex hormones play an important role in maintaining bone health, and there are concerns that some hormonal contraceptive, depot medroxyprogesterone acetate in particular, may adversely affect bone mass accrual in some women [94]. As discussed earlier in this review, most women using the LNG-IUS have ovulatory cycles and E2 levels remaining within the range of a normal menstrual cycle [4]. As such, at present, there is no plausible mechanistic action that would suggest a deleterious effect on bone health. Indeed, the
available data for the LNG-IUS generally suggest that it has no adverse effect on bone mineral density (BMD).

A comparison of BMD in women who had used the LNG-IUS \( (n=53) \) for 7 years compared with age- and body mass index-matched copper IUD users as controls showed no significant differences between the groups in BMD at midshaft of the ulna \( (0.469\pm0.008 \text{ and } 0.467\pm0.009 \text{ g/cm}^2, \text{ respectively; } p=0.82) \) and distal radius \( (0.409\pm0.009 \text{ and } 0.411\pm0.009 \text{ g/cm}^2, \text{ respectively; } p=0.84) \) [95]. In a further study, where women \( (n=37) \) who had their old LNG-IUS removed and a new one placed, no significant difference in BMD was found at midshaft of the ulna \( (0.456\pm0.009 \text{ and } 0.469\pm0.008 \text{ g/cm}^2, \text{ respectively; } p=0.51) \) after a total of 10 years of use compared to matched controls using the copper IUD [96].

3.4.9. Cardiovascular effects

The LNG-IUS may be used in women with a history of venous thromboembolism or pulmonary embolism as the advantages gained generally outweigh the risk of these events [92,93,97]. The LNG-IUS was observed to decrease activated protein C resistance, suggesting that it does not have prothrombotic effects [98]. A general population-based study in 2814 women from a Northern Finland birth cohort comparing the effects of LNG-IUS and oral contraceptive use on metabolic, cardiovascular and inflammatory parameters showed that LNG-IUS did not adversely affect the profile of these parameters [99]. In contrast, oral contraceptive use resulted in changes that would be consistent with a potential increased future risk of cardiovascular and metabolic disease. In a randomized controlled study comparing the effect of LNG-IUS use \( (n=46) \) with a copper IUD use \( (n=46) \) on lipid metabolism in Asian women, marginal reductions in total cholesterol levels were observed in the LNG-IUS group but not the copper IUD group over 18 months of use [100]. Other lipid parameters generally remained unaffected and stable relative to baseline in both groups. In addition, apolipoprotein A1 and apolipoprotein B levels remained relatively stable. Consistent with the limited negative impact on these surrogate parameters, a Danish national cohort study assessing the risk of venous thrombosis in current users of various hormonal contraception conducted between 1995 and 2005 showed that LNG-IUS did not confer any increased risk of venous thrombosis compared to nonusers (adjusted rate ratio 0.89; 95% CI 0.64–1.26) [101].

3.4.10. Breast and uterine cancer

The use of the LNG-IUS is contraindicated in women with breast cancer and other hormone-dependent cancers. However, a comparison of 165 breast cancer cases from the large Finnish postmarket study with data on breast cancer diagnoses from the Finnish Cancer Registry suggested that the use of the LNG-IUS was not associated with an increased risk of breast cancer relative to the Finnish female population [102]. Similarly, ever or current use of the LNG-IUS was not associated with an increased risk of breast cancer compared with ever or current use of copper IUDs in a population-based, case-controlled study of 5113 confirmed cases in Finland and Germany [103]. The adjusted odds ratio for ever users of the LNG-IUS versus ever users of copper IUDs was 0.99 (95% CI 0.88–1.12), with a corresponding odds ratio of 0.85 (95% CI 0.52–1.39) for current users at time of diagnosis.

The recurrence of breast cancer was investigated in a retrospective, controlled cohort study of 79 women using the LNG-IUS and a comparison group of 120 women with no history of using the LNG-IUS [104]. There was no increased risk of breast cancer recurrence with use of the LNG-IUS (adjusted hazard ratio 1.86; 95% CI 0.86–4.00). However, a subgroup analysis revealed a higher risk of recurrence, of borderline significance, in women who developed breast cancer while using and continuing to use the LNG-IUS compared with the comparison group (adjusted hazard ratio 3.39; 95% CI 1.01–11.35; \( p=0.048 \)). No significant difference was reported in the subgroup of women who used the LNG-IUS after the diagnosis of breast cancer compared to the comparison group (adjusted odds ratio 1.48; 95% CI 0.62–3.49; \( p=0.38 \)). However, the numbers in the LNG-IUS subgroups were small, and disease severity varied across the two LNG-IUS subgroups. For example, nearly half (47.4%; 18/38) of the patients in the subgroup who developed breast cancer while using and continuing to use the LNG-IUS had nodal involvement compared with 29.3% (12/41) of those who used the LNG-IUS after the diagnosis of breast cancer, suggesting a potential for an increased risk of recurrence in the former LNG-IUS group. All patients with breast cancer recurrence had metastatic disease.

A systematic review and meta-analysis of 24 observational studies in 1001 women showed that the LNG-IUS was more effective than oral progestins in inducing regression of endometrial hyperplasia [105]. In women treated with tamoxifen for breast cancer, the use of LNG-IUS reduced the occurrence of de novo endometrial polyps as well as hyperplasia [106,107]. Indeed, the LNG-IUS prevents endometrial polyps with continued use in women taking tamoxifen for up to 4.5 years [108].

4. Cost-effectiveness of the LNG-IUS

The information on the cost-effectiveness of the LNG-IUS as a contraceptive is limited to the National Health Service (NHS) perspective in the UK [36,65,109] or the payer perspective in the USA [110,111], with only one study reporting cost-effectiveness from the US societal perspective [112]. From the UK NHS perspective, copper IUDs and implants tended to have the better cost-effectiveness profiles relative to LNG-IUS especially over the first few years of use [36,65,109]. Until recently, the LNG-IUS was shown to be
one of the most cost-effective methods of contraception from the payer perspective in the USA over 5 years of use [110,111]. However, ongoing cost-effectiveness of any contraceptive would be sensitive to disproportionate changes in underlying cost estimates included in the analysis, and the recent price increases of the LNG-IUS in the USA have altered the relative cost-effectiveness profile of the LNG-IUS relative to other contraceptives in the USA [113]. From the US societal perspective, depot medroxyprogesterone acetate appears to dominate (i.e., lower associated cost and more quality-adjusted life-years gained) with the LNG-IUS and copper-IUD over 2 years [112].

4.1. Quality of life and satisfaction associated with the use of the LNG-IUS

There are very limited data regarding the effects of using the LNG-IUS on quality of life in women using it mainly for contraception. One study compared the effect of the LNG-IUS with other IUDs or no contraception on the quality of life and sexual functioning of Polish women [114]. Quality of life outcomes in the LNG-IUS group were higher than for both comparison groups in the general health (p<.001), energy/fatigue (p<.01) and emotional well-being domains (p<.001). Moreover, the LNG-IUS had a beneficial effect on sexual desire and arousal (both p<.05) compared to other IUDs or no contraception.

The LNG-IUS is generally well received in clinical practice, and most women who use it are satisfied. In the large Finnish postmarket survey of over 17,000 women, 74% were satisfied with the LNG-IUS, with satisfaction increasing with age [37]. A Spanish survey of 1154 women who had used the LNG-IUS for at least 2 years reported that 94% of respondents were satisfied with it [115]. A postmarket survey across 14 European countries (including some from Eastern Europe) showed that satisfaction with the current method of contraception was highest with the LNG-IUS, with 79% of the 404 respondents being satisfied [116]. Another survey of 8680 women in 18 countries across Europe and the Near East found that the vast majority (95%) of LNG-IUS users were satisfied with their IUS, increasing to 99% among those using their second LNG-IUS [117].

5. Conclusions

The LNG-IUS is a well-established, highly effective reversible contraceptive method. Available data suggest that continuation rates in clinical practice tend to be slightly higher than rates reported in clinical trials, and user satisfaction and continuation with the LNG-IUS may be further improved with counseling. The LNG-IUS is typically associated with transient menstrual disturbance during the first few months of use, but this usually settles with continued use, with a concomitant decrease in menstrual blood loss. In addition, transient menstrual disturbance does not reoccur in women who opt for a subsequent LNG-IUS after 5 years of use provided that the old LNG-IUS is replaced immediately. Uterine perforation during LNG-IUS placement is a rare complication, which may be increased during lactation and the postpartum period. Overall, the safety profile of the LNG-IUS has been well established across a wide population of women, and the available data do not suggest that the LNG-IUS adversely affects bone health or increases the risk of adverse cardiovascular events or breast and uterine cancers. There is a rapid return to fertility following removal of the LNG-IUS in women wanting to conceive, with 1-year pregnancy rates similar to otherwise fertile women proactively using ‘natural family planning’ to conceive.

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