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EXPERT REVIEWS

Safety and efficacy of the levonorgestrel-releasing intrauterine system: recent insights

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This overview focuses on the recent developments in the safety and efficacy of the levonorgestrel-releasing intrauterine system (LNG-IUS) on established indications, namely contraception, treatment of heavy menstrual bleeding as well as endometrial protection during estrogen therapy for menopausal symptoms. The LNG-IUS is one of the most efficacious reversible contraceptive methods available. It can be used by various patient groups, including nulliparous women, during breast-feeding, after elective pregnancy termination, in women suffering from various pre-existing medical conditions and menopausal women. This review provides an overview of the published literature on the LNG-IUS from the last 5 years, focusing on cost–effectiveness, safety-related outcomes, the use of LNG-IUS by young and/or nulliparous women as well as by various different patient groups. After decades of dominance by the 'the Pill', it is likely that in the future, long-acting reversible contraceptives, such as the LNG-IUS, will become the first-line contraceptive options, owing to their superior contraceptive effectiveness in real-life use, cost–effectiveness as well as their established safety profile.

Keywords: contraception • heavy menstrual bleeding • intrauterine contraceptive device • levonorgestrel • levonorgestrel-releasing intrauterine system • progestogens

The levonorgestrel-releasing intrauterine system (LNG-IUS) was first introduced in Finland in 1990, followed by more than 120 countries worldwide. The main indications of the LNG-IUS include contraception, treatment of heavy menstrual bleeding (HMB) and endometrial protection during estrogen replacement (last indication not approved in all countries). Since its launch, numerous publications and reviews have demonstrated the high efficacy and acceptability of the LNG-IUS in these indications [1]. Until recently, 'the Pill' has been the standard for contraception among young women. However, today the advantages of long-acting reversible contraceptives (LARCs), such as subdermal implants and intrauterine contraceptive devices (IUCDs), including copper-releasing IUDs (Cu-IUDs) and the LNG-IUS, are being increasingly recognized. An increasing number of women in Europe and in the USA use LARCs, and the LNG-IUS and Cu-IUDs are the most popular contraceptives in this class [2–4]. The same is true for women with intercurrent health problems, for whom combined contraceptives containing estrogen and progestin may potentially increase health risks [5].

The present review provides an overview of published data from the last 5 years and is an update of a previous review on the established indications of the LNG-IUS [6]. A review of emerging indications for LNG-IUS use has previously been published [7].

Material & methods

A PubMed search (data locking point 27 August 2012) was performed with the following search terms: levonorgestrel-releasing or Mirena® (Bayer, Leverkusen, Germany) or intrauterine system with the following limits 'English language only and published within the last 5 years'. This resulted in 629 articles, which were manually searched by the authors; the most relevant articles were included by joint decision. Studies not relating to humans were excluded. Furthermore, case reports or small case series

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were not included in the review as they were not considered to represent robust evidence.

Results

Cost–effectiveness of the LNG-IUS when used for contraception

Cost–effectiveness and a health economics perspective is a high priority today. Considerable cost savings both from an individual and a wider health economics perspective can be achieved with effective and acceptable contraceptive methods that help to reduce unwanted pregnancy and from improving menstrual-related bleeding problems. Contraceptive efficacy of the LNG-IUS is comparable to that of female sterilization and has been reported to be equal in all age groups [1]. In a review on articles published over the last two decades on various types of IUCDs (including Cu-IUDs, such as Multiload [Merck, NJ, USA], NovaT [Bayer, Leverkusen, Germany], ParaGard T-380A [Duramed Pharmaceuticals, Inc., NJ, USA] and the LNG-IUS), excellent effectiveness of IUCDs with a global cumulative pregnancy rate of <2% after 5 years of use was observed whatever the type of device [1]. However, the LNG-IUS was the most effective with a cumulative pregnancy rate at 5 years of <0.5% [1]. Higher effectiveness of LARCs in real-life use, regardless of age and other user characteristics, compared with the contraceptive pill, patch or ring, was also confirmed in a recent cohort study from the USA [2]. In the USA, the number of women undergoing surgical sterilization has been reduced due to the introduction of LNG-IUS [8]. High efficacy (no pregnancies) and high level of user satisfaction (84%) were also reported in a prospective clinical study including 509 women over 12 months of use in the USA [9]. Primary reasons for premature discontinuation were expulsion (4.5%) and menstrual cycle problems (3.8%) [9].

According to two cost–effectiveness analyses from the UK and Spain (not including costs for potential contraceptive side effects, noncontraceptive benefits and quality of life changes), LARCs are more cost effective than injectables or oral contraceptive pills and condoms after only 1 year of use [10,11].

Cost–effectiveness of the LNG-IUS when used for HMB

Treatment of HMB with the LNG-IUS has been shown to be cost effective in various countries and settings [12]. A systematic review and meta-analysis of clinical outcomes of treatments for HMB showed a similar degree of improvement of health-related quality of life with LNG-IUS compared with first- or second-generation endometrial ablation (EA) techniques [12]. Cost–effectiveness analysis of hysterectomy versus first- and second-generation EA techniques and the LNG-IUS was analyzed in two reviews [13,14]. The few data available suggest that the LNG-IUS is more cost effective than first-generation EA techniques with satisfaction being similar to that of second-generation EA techniques. Limited evidence suggested that hysterectomy is preferable to the LNG-IUS [12]. However, the long-term risk of pelvic floor surgery and urinary incontinence is higher in women treated by hysterectomy than by EA or the LNG-IUS. Although it may be the most cost-effective strategy in some settings, hysterectomy may not be considered an initial or acceptable option for many patients, owing to its invasive nature and higher risk of complications.

Repeat use of the LNG-IUS

Repeat LNG-IUS use is increasing worldwide on several indications [15]. Insertion of a second consecutive LNG-IUS after 5 years of use of the first LNG-IUS was judged to be easy and associated with no or mild pain in a vast majority of women [16,17]. Of special clinical impact was the finding that the initial irregular bleeding pattern frequently observed with a first LNG-IUS could be avoided if the second LNG-IUS was inserted immediately. This practice also resulted in further reduction of bleeding and spotting and an increased rate of amenorrhea compared with the rate observed during the use of the first LNG-IUS [18]. Interestingly, in the European setting, the highest satisfaction was seen among the women reporting amenorrhea. However, the acceptability of contraception-induced amenorrhea may vary according to cultural and other characteristics of the women.

Mode of action of LNG-IUS when used for contraception or HMB

Quality and sperm penetrability of mid-cycle cervical mucus from LNG-IUS users and hormone-free controls was compared *in vitro* in a double-blinded fashion [19]. It was shown that mid-cycle cervical mucus of LNG-IUS users was of poor quality and thus prevented endocervical sperm transport, confirming earlier studies that this is the main mechanism of contraceptive action of the LNG-IUS. Thus, the contraceptive action of the LNG-IUS happens before fertilization, which is an important counseling aspect.

The endometrial suppression is responsible for the reduced bleeding and thus the therapeutic effect in treatment of HMB. This is associated with an increase in uterine artery resistance index in LNG-IUS users, which is not observed in Cu-IUD users [20].

LNG-IUS after abortion

The safety and efficacy of immediate postabortal placement of the LNG-IUS has earlier been demonstrated by several studies. However, some clinicians may still have concerns over this topic and most previous data refers to early surgical termination of pregnancy. In a recent randomized controlled trial (RCT) comparing immediate versus delayed (3–6 weeks after surgery) placement after elective second trimester pregnancy termination, expulsion rates were similar (6.8 and 5.0%, in the immediate and delayed groups, respectively, $p = 1.0$), and there were no marked differences in other adverse events, either [21]. However, only 45.5% of the women randomized to delayed insertion actually returned to the placement visit, and thus significantly more women had the LNG-IUS placed in the immediate rather than in the delayed placement groups. This highlights the importance of starting contraception as soon as possible after elective pregnancy termination. Thus, even though the expulsion rate may be somewhat increased (in particular after second trimester abortions),

immediate insertion should be encouraged at the time of surgical first or second trimester abortion [21–23].

There are less studies concerning insertion of IUCD after medical abortion. An ideal time for IUCD placement may be the day a woman presents for verification of a completed medical abortion, which is usually performed at 1–3 weeks after treatment. In earlier studies of IUCD use following medical abortion, the devices have been inserted either at 2–3 weeks after abortion or at the time of first postabortal menstruation [24]. Recently, the Cu-IUD was shown to be inserted in a safe manner during the first week after the medical abortion [25]. The same was shown to be true for the LNG-IUS [26]. Significantly, more women returned for insertion among those scheduled for early insertion to be performed within 1 week of the abortion treatment than those scheduled for delayed insertion at 3 weeks following the abortion. Furthermore, more women with a LNG-IUS reported reduced bleeding postabortion compared with women a Cu-IUD.

The efficacy of IUCD in the prevention of a repeat abortion has been studied in several cohorts and population-based studies [27–32]. All these studies showed that IUCD is more effective in preventing repeat abortions than oral contraception [28,29,32] or other non-intrauterine contraception [27]. Thus, postabortion insertion of IUCD and especially the LNG-IUS seems to be an effective means to avoid repeated unwanted pregnancy and induced abortion.

Is early insertion of the LNG-IUS after delivery feasible?

The first year postpartum is a period of high risk for unintended pregnancy. Therefore, immediate (within 10 min following delivery of the placenta) postpartal insertion of IUCD has been presented as an option to start effective contraception immediately after delivery. Immediate Cu-IUD insertion has been shown to be safe when compared with later postpartum time periods and interval insertion. For Cu-IUD, increased expulsion rates were noted with delayed postpartum insertion, compared with immediate insertion and with immediate insertion, compared with interval insertion [33]. The placement of the LNG-IUS immediately after delivery has been assessed in four studies [34–37]. In two RCTs, postplacental versus delayed insertion of the device or insertion at three time points, immediate (within 10 min of placenta delivery), early (10 min to 48 h postpartum) [34] or interval (≥6 weeks postpartum) [35], were compared. Expulsion rate was significantly higher in the immediate (postplacental) than in the delayed insertion group; at 6-month follow-up, expulsion had occurred in 12 of 50 versus two of 46 (i.e., 24 vs 4%; $p = 0.008$) of women in the early and delayed groups, respectively [35]. When lost devices were replaced, the rate of LNG-IUS use observed at 6 months was similar in both groups. This is in agreement with the other RCTs including 46 women; no differences in rates of LNG-IUS at 3 and 6 months were seen between early compared with late insertion groups [36]. Rates of expulsion were significantly higher in the early and immediate groups compared with the interval group. However, pain during insertion was significantly higher in the interval group ($p < 0.001$) when compared to the other groups [36]. In a case series including 40 women, 29 women received the LNG-IUS at a median of 20 h (range: 7–48 h) after delivery. Eleven women (38%) had a spontaneous expulsion [31]. A pilot study included 20 women and insertion was carried out under ultrasonographic guidance at a median time from placental delivery to insertion of 5.5 min. No perforations were reported. At 10-week follow-up, the expulsion rate was 10.5% [37].

One RCT reported on the effects of immediate postplacental versus delayed LNG-IUS insertion on the patterns of breast-feeding [38]. Breast-feeding was initiated by 64% (32 out of 50) of the women randomized to immediate versus 58% (27 out of 46) in the group of delayed insertion. However, at 6-month follow-up, significantly, fewer women (6 vs 24%; $p = 0.02$) in the group of immediate insertion continued breast-feeding [38]. These results are in contrast with the generally viewed safety of progestin-only contraceptive use during lactation as well as previous studies assessing the use of the LNG-IUS during lactation [39].

Thus, postplacental insertion of the LNG-IUS is a possible option although available studies consistently report increased expulsion rates compared with interval insertion. In addition, more data are needed on the possible impact of LNG-IUS on breast-feeding.

Use of the LNG-IUS in special patient groups

The LNG-IUS has several features, such as reduction in menstrual bleeding and a lower incidence of pelvic inflammatory disease compared with Cu-IUD, which may make it an ideal contraceptive method for women with underlying medical condition(s) such as diabetes mellitus [40], women living with HIV/AIDS [41] or in women at increased risk of bleeding due to either inherited bleeding disorders [42] or to the use of anticoagulation [43,44]. In these studies, the LNG-IUS has behaved similarly as in healthy women, and has been associated with reduced uterine bleeding, increased blood hemoglobin levels, and most importantly, no effect on the course of the underlying disease [41].

The use of the LNG-IUS versus no intervention has been compared in a RCT performed in women taking anticoagulant therapy after cardiac valve surgery [44]. Similar to what has been observed in healthy women, vaginal bleeding was reduced and hemoglobin levels increased within 3 months of LNG-IUS use. Coagulation factors were unaffected by the LNG-IUS [44]. Also, when the LNG-IUS is used purely for contraception, it is accompanied with an increase of hemoglobin and ferritin, which may be especially important in women with underlying medical conditions [45].

Another emerging patient group with special needs are obese women. Use of the LNG-IUS in women with BMI exceeding 30 kg/m^2 suffering from abnormal uterine bleeding resulted in reduced menstrual bleeding and high subject satisfaction [46]. In addition, the uptake of the LNG-IUS has been shown to be high in morbidly obese women undergoing bariatric surgery [47].

New data regarding the safety & metabolic effects of the LNG-IUS

Several studies, which addressed various safety-related outcomes among LNG-IUS users, were published within the last 5 years and

Table 1. Recent articles describing safety-related outcomes in levonorgestrel-releasing intrauterine system users.

Study (year)	Topic	Methodology	Main findings	Ref.
Brahmi *et al.* (2012)	Pregnancy with IUCD *in situ*	Review of nine publications reporting on pregnancy outcomes with IUCD *in situ*	Women with retained IUDs were at the greatest risk of adverse pregnancy outcomes, including spontaneous abortion, preterm delivery, septic abortion and chorioamnionitis. IUCD removal decreased risks but not to the baseline risk of pregnancies without an IUCD	[48]
Bahamondes *et al.* (2006)	BMD	Cross-sectional study on LNG-IUS, comparison with matched cohort of copper IUD users	Forearm BMD in LNG-IUS users similar in copper IUD users	[49]
Bahamondes *et al.* (2010)		Prospective study on long-term LNG-IUS vs copper IUD users	Forearm BMD in LNG-IUS users similar as in copper IUD users	[50]
Ferreira *et al.* (2010)	Cardiovascular risk markers	RCT on blood pressure and lipid metabolism in LNG-IUS vs GnRH analog users in endometriosis	Both treatments had no effect on blood pressure. LNG-IUS users had lower total cholesterol and triglyceride values	[51]
Heliövaara-Peippo *et al.* (2011)		RCT of LNG-IUS vs hysterectomy in women with HMB with 10-year follow-up, primary outcome HRQoL	Both treatments had no effect on blood lipids, but there was an increase in serum inflammatory markers (such as high sensitivity CRP) in the hysterectomy group	[52]
Ng *et al.* (2009)		RCT of LNG-IUS vs copper IUD on lipid metabolism	LNG-IUS user was associated with no adverse effects on lipid metabolism	[53]
Morin-Papunen *et al.* (2008)		Population-based study of LNG-IUS vs OC and no hormonal contraceptive users on CVD risk markers & insulin sensitivity	LNG-IUS use was not associated with adverse effects on blood pressure, lipid profile, CRP levels or insulin sensitivity, compared with users of nonhormonal contraception	[54]
Kayikcioglu *et al.* (2006)		Prospective study in LNG-IUS users with HMB on CVD risk markers and metabolic parameters	LNG-IUS was associated with no adverse effects on lipid metabolism or liver function tests. Diastolic blood pressure decreased, fasting glucose significantly increased	[55]
Lidegaard *et al.* (2012)	VTE	Registry-based epidemiological study on first-time VTE in users of non-oral contraceptive methods, compared with nonhormonal method users	LNG-IUS use was associated with a significantly decreased risk of VTE, compared with nonhormonal method use	[56]
Lidegaard *et al.* (2012)	Arterial thrombosis	Registry-based epidemiological study on stroke and myocardial infarction in users of various contraceptive methods, compared with nonhormonal method users	LNG-IUS use was not associated with an increased risk of stroke or myocardial infarction, compared with nonhormonal method use	[57]
Lessard *et al.* (2008)	Vaginal flora and cervical cytology	Prospective study on cervical cytology and vaginal flora in long-term LNG-IUS users	No increase in cytopathological abnormalities, BV or *Trichomonas vaginalis* incidence	[58]
Neale *et al.* (2009)		Prospective comparison of vaginal smears of LNG-IUS users an copper IUD users	Copper-releasing IUD users were more likely than LNG-IUS users to have abnormal vaginal flora and BV	[59]

BMD: Bone mineral density; BV: Bacterial vaginosis; CRP: C-reactive protein; CVD: Cardiovascular disease; FSFI: Female sexual function index; GnRH: Gonadotropin-releasing hormone; HMB: Heavy menstrual bleeding; HRQoL: Health-related quality of life; HT: Hormone therapy; IUCD: Intrauterine contraceptive device; LNG-IUS: Levonorgestrel-releasing intrauterine system; OC: Oral contraception; RCT: Randomized controlled trial; VTE: Venous thromboembolism.

Table 1. Recent articles describing safety-related outcomes in levonorgestrel-releasing intrauterine system users (cont.).

Study (year)	Topic	Methodology	Main findings	Ref.
Donders *et al.* (2011)		Prospective study on cervical cytology in LNG-IUS users	Occurrence of abnormal vaginal flora, BV, aerobic vaginitis or *Candida* vaginitis not increased compared to preinsertion	[60]
Kaliterna *et al.* (2011)		Comparison of IUCD users vs noncontraceptors	*Escherichia coli* and *Ureaplasma urealyticum* more often isolated from IUCD users than noncontraceptive method users	[61]
van Grootheest *et al.* (2011)	Uterine perforation	Retrospective case series of uterine perforations	Abdominal pain and control visit were the most common reasons leading to diagnosis of uterine perforation. Uterine perforation may be asymptomatic and remain undetected	[62]
Kaislasuo *et al.* (2012)		Population-based study on uterine perforations treated surgically in Finland	Estimated perforation rate with both copper IUDs and LNG-IUS was 0.4/1000 insertions. More than half of women who experienced perforation had delivered within 6 months and one out of three were breast-feeding at time of placement	[63]
Merki-Feld *et al.* (2008)	Expulsion	Retrospective analysis of clinical records of LNG-IUS and copper IUD users	Lower risk of device dislocation was observed in LNG-IUS users, compared with copper IUD users. History of expulsion was associated with higher risk of re-expulsion	[64]
Bahamondes *et al.* (2011)		Prospective comparison of LNG-IUS and copper IUD users	Expulsion rates were in 2.2% of LNG-IUS users and 5.5% of copper IUD users	[65]
Skrzypulec and Drosdzol (2008)	Sexual function	Cross-sectional analysis of LNG-IUS and copper IUD users using FSFI	Prevalence of female sexual dysfunction was lower among LNG-IUS vs copper IUD users	[66]
Witting *et al.* (2008)		Epidemiological study of FSFI in a population sample	LNG-IUS was associated with less pain, more desire, arousal, satisfaction, compared with other contraceptive methods	[67]
Halmesmäki *et al.* (2007)		RCT of LNG-IUS vs hysterectomy in women with HMB	McCoy scale in LNG-IUS users showed no change over 5 years with the exception of deterioration of satisfaction with partner	[68]
Bastianelli *et al.* (2011)		Single-group prospective study of LNG-IUS users	FSFI score showed improvement in desire and pain, while other domains remained unchanged	[69]
Enzlin *et al.* (2012)		Cross-sectional study of LNG-IUS and copper IUD users using the short sexual functioning scale	LNG-IUS users had similar psychological and sexual functioning compared with copper IUD users. Overall, the influence of IUCD on sexual functioning was small	[70]

BMD: Bone mineral density; BV: Bacterial vaginosis; CRP: C-reactive protein; CVD: Cardiovascular disease; FSFI: Female sexual function index; GnRH: Gonadotropin-releasing hormone; HMB: Heavy menstrual bleeding; HRQoL: Health-related quality of life; HT: Hormone therapy; IUCD: Intrauterine contraceptive device; LNG-IUS: Levonorgestrel-releasing intrauterine system; OC: Oral contraception; RCT: Randomized controlled trial; VTE: Venous thromboembolism.

Table 1. Recent articles describing safety-related outcomes in levonorgestrel-releasing intrauterine system users (cont.).

Study (year)	Topic	Methodology	Main findings	Ref.
Heliövaara-Peippo *et al.* (2010)	Urinary tract symptoms, lower abdominal/pelvic pain	RCT of LNG-IUS vs hysterectomy in women with HMB	Compared with hysterectomy, LNG-IUS was associated with less urinary tract symptoms and incontinence	[71]
Heliövaara-Peippo *et al.* (2009)		RCT of LNG-IUS vs hysterectomy in women with HMB	Lower abdominal pain score decreased in both groups, but back pain score decreased only with LNG-IUS	[72]
Trinh *et al.* (2008)	Breast cancer	Retrospective controlled cohort analysis on recurrence rate in women diagnosed with breast cancer	Overall, no increased risk of breast cancer recurrence associated with the LNG-IUS	[73]
Dinger *et al.* (2011)		Retrospective, population-based case–control study in women <50 years comparing breast cancer risk in LNG-IUS and copper IUD users	LNG-IUS was associated with no increased risk of breast cancer compared with copper IUD use	[74]
Lyytinen *et al.* (2010)		Retrospective registry-based case–control study in postmenopausal women using various types of HT	Increased risk of breast cancer risk among the LNG-IUS + estrogen and the LNG-IUS-only users	[75]
Jaakkola *et al.* (2011)	Endometrial cancer	Retrospective registry-based case–control study in postmenopausal women using various types of HT	Decreased risk of endometrial cancer risk among the LNG-IUS + estrogen and the LNG-IUS-only users	[76]

BMD: Bone mineral density; BV: Bacterial vaginosis; CRP: C-reactive protein; CVD: Cardiovascular disease; FSFI: Female sexual function index; GnRH: Gonadotropin-releasing hormone; HMB: Heavy menstrual bleeding; HRQoL: Health-related quality of life; HT: Hormone therapy; IUCD: Intrauterine contraceptive device; LNG-IUS: Levonorgestrel-releasing intrauterine system; OC: Oral contraception; RCT: Randomized controlled trial; VTE: Venous thromboembolism.

these are summarized in Table 1 [48–76]. Pregnancy with IUCD or LNG-IUS *in situ* was analyzed in one review [48], which reconfirmed the already established medical knowledge that an IUCD left *in situ* during pregnancy increases various pregnancy complications irrespective of the type of IUCD (Table 1). Removal of the IUCD decreased these risks but not to the expected background frequency of women without an IUCD at the start of pregnancy.

Two studies reported on bone mineral density during the use of the LNG-IUS and neither found a difference between the LNG-IUS and Cu-IUD users [49,50].

Several studies reported on the cardiovascular disease risk markers and metabolic effects in LNG-IUS users (Table 1). In general, these were consistent with no clinically significant effects (Table 1). Regarding glucose tolerance, one study described slightly increased fasting blood glucose in premenopausal women, however, impaired glucose tolerance was not diagnosed [55].

Two registry-based studies have analyzed the risk of venous thromboembolism [56] and arterial cardiovascular complications (stroke and myocardial infarction [seven in LNG-IUS users]) [57]. Since the exact exposure to LNG-IUS in this study was not known due to the unavailability of information regarding the date of removal, the authors assumed 3-year exposure from the date of prescription. However, this could have led to an underestimation of the actual exposure due to the fact that LNG-IUS is licensed for 5 years of use. Nevertheless, the LNG-IUS was not associated with an increased risk of either venous or arterial thrombotic events (Table 1). In contrast, LNG-IUS use was associated with a significantly decreased risk of venous thromboembolism compared with nonhormonal method users, a finding which, however, lacks biological plausibility as pointed out in the so-called rapid responses to this article [101].

The effect of LNG-IUS on the vaginal flora and cervical cytology was studied in four publications using different methodologies (Table 1). In general, no increase in the incidence of bacterial vaginosis or cytological abnormalities was found.

Two studies reported on uterine perforation associated with IUCD [62,63]. The first study analyzed spontaneous adverse drug reaction reports, thus the denominator – in this case the number of insertions or women-years is not known, preventing calculation of incidence rates [62]. Only in approximately 40% of reports was information provided regarding symptoms leading to the diagnosis of perforation; the most frequent symptoms being abdominal pain and abnormal bleeding [62]. Of the women known to be parous, approximately 42% were breast-feeding at the time when perforation was diagnosed [62]. Kaislasuo *et al.* reported the estimated uterine perforation rate of approximately 0.4 per 1000 insertions in a population-based study in Finland, which was similar in the LNG-IUS and Cu-IUD users [63]. A total of 55% of women experiencing uterine perforation had their IUCD placed <6 months after the delivery, and approximately one out of three were breastfeeding at the time of placement. However, it was not possible to calculate the magnitude of the possibly increased risks of uterine perforation in postpartum or breastfeeding women, as the denominator (i.e., total population of women postpartum or

breastfeeding) was not known. Importantly, neither publication reported any cases of serious or permanent sequelae from the uterine perforations.

Two studies reported a lower expulsion and/or dislocation rate in LNG-IUS users, compared with Cu-IUD users (Table 1), but the overall expulsion rates were low in both groups, and it is not clear if the studies were sufficiently powered to detect small differences.

In general, LNG-IUS was reported to have a neutral effect on sexual function although one study suggests that sexual function may be better in LNG-IUS users, compared with Cu-IUD users, and two studies found an improvement in desire and pain domains of the female sexual function index during LNG-IUS use (Table 1).

Symptoms of the lower urinary tract and pelvic/lower abdominal pain were reported among women treated for HMB by the LNG-IUS or hysterectomy (Table 1). Compared with LNG-IUS use, hysterectomy increased the risks for incomplete emptying, lower urinary tract infections and stress urinary incontinence. Hysterectomy as well as LNG-IUS decreased lower abdominal pain, while only LNG-IUS use could reduce back pain.

Three studies have analyzed the risk of breast cancer in users of the LNG-IUS. One study which compared women diagnosed with breast cancer and with prior or no use of LNG-IUS found that ever-use of LNG-IUS was not associated with increased risk of breast cancer recurrence in women diagnosed with breast cancer [73]. In a sub-analysis, a marginally higher recurrence rate was found among women who developed breast cancer during the use of LNG-IUS and continued its use after the diagnosis compared with women diagnosed with breast cancer who did not use the LNG-IUS [73]. In contrast, in a subanalysis, where patients who started their LNG-IUS use only after completion of primary treatment for breast cancer and were using antiestrogen adjuvant therapy, no increased risk of recurrence of breast cancer was observed compared with women diagnosed with breast cancer and with no use of the LNG-IUS [73]. However, it should be remembered that according to the WHO Medical Eligibility Criteria for Contraceptive Use, the use of LNG-IUS is contraindicated (category 4) for women with current breast cancer. Whereas, its use is category 3 (use of method not usually recommended unless other more appropriate methods are not available or not acceptable) for women with a personal history of breast cancer and no evidence of current disease for 5 years [102].

Two case–control studies examined the risk of the development of breast cancer during the use of the LNG-IUS. One study found no increase in breast cancer incidence (either tumor induction or promotion) associated with LNG-IUS use when compared with Cu-IUD use in women <50 years of age [74]. This was seen in both crude analyses and after adjusting for known risk factors for breast cancer. This is consistent with an earlier reported cohort study [77]. The second study focused on postmenopausal women using estrogen treatment for climacteric symptoms with cross-linking of cancer registry diagnoses with the national drug reimbursement registry [75]. An increased risk of breast cancer was associated with the LNG-IUS and estrogens, but also LNG-IUS-only use. However, information on several known risk factors for breast cancer was not available in this study and thus could not be adjusted for. Also, the information of exposure was an estimate based on the reimbursement registry without knowledge of actual insertion and removal of the LNG-IUS [75]. Therefore, the results regarding breast cancer risk when the LNG-IUS is used for endometrial protection during estrogen treatment must be interpreted with caution and further studies in postmenopausal women are warranted to confirm or refute the results.

Taken together, current data support that there is no increased risk of primary diagnosis of breast cancer among premenopausal women who use the LNG-IUS, while the risk remains unknown in women using the LNG-IUS together with estrogens for HRT.

Using similar methodology, one study reported on the risk of development of endometrial cancer associated with different types of hormone therapy (HT) regimens, including the LNG-IUS, by postmenopausal women [76]. A decreased risk of endometrial cancer development in users of estrogen therapy (ET) + LNG-IUS, as well as LNG-IUS-only users, was found.

The use of the LNG-IUS in nulliparous women

Wider use of LARCs would be an effective strategy to prevent unplanned pregnancies, and with improved contraceptive counseling, the uptake of LARCs can be increased [78]. Due to its efficacy and additional health benefits, the use of the LNG-IUS among young nulliparous women is expanding rapidly, although there is considerable variation between countries (Table 2) [15,79–86]. In the USA, the recommended patient profile for the LNG-IUS includes 'women who have had at least one child' – however, such general restrictions regarding use in nulliparous women are not in place in the countries where the LNG-IUS is marketed the most. Adolescents and nulliparous women are not more likely to prematurely discontinue use of their IUS than adult or parous women [86]. Recent studies have confirmed that the LNG-IUS can also be used for reduction of dysmenorrhea and HMB by young and nulliparous women (Table 2).

The fact that three out of seven studies on the use of LNG-IUS by nulliparous women focused on the insertion procedure indicates that it may be perceived as challenging in this group of women (Table 2). However, in a majority of women, insertion was regarded as technically easy by the healthcare provider and no perforations were reported. Despite the fact that the insertion was experienced as painful by a large proportion of women, this did not negatively influence satisfaction with the LNG-IUS [80]. Compared with 'older' women or parous women, young or nulliparous women were not more likely to have their IUS removed because of dissatisfaction (Table 2) [86]. The most common reason for removing the IUS was wish for pregnancy. Return to fertility and 1-year pregnancy rates after removal of the LNG-IUS did not differ from those seen after session of barrier methods or use of no contraceptives [87].

Taken together, there is increasing evidence to support that the LNG-IUS is a safe and well accepted, highly effective contraceptive method for young and nulliparous women as well as older women. Additional therapeutic effects include reduced HMB and dysmenorrhea.

Table 2. Recently published studies on the use of the levonorgestrel-releasing intrauterine system in young, nulliparous women.

Study (year)	Topic	Methodology	Main findings	Ref.
Bahamondes *et al.* (2011)	Insertion	Retrospective case–control study nulligravida (n = 159) vs parous women (n = 477)	Insertions judged as easy by >80% of providers, with total failures of <1% and expulsions of 4%	[79]
Marions *et al.* (2011)	Insertion	Noninterventional study, nulliparous women (n = 224), 12–16 weeks of follow-up	Insertions judged as easy by 72% of providers; 2.6% failed insertions; pain judged as none (9%), moderate (72%) or severe 17%. No perforations or pregnancies. At 12–16 weeks, at 1-year follow-up, 76% satisfied	[80]
Brockmeyer *et al.* (2008)	Insertion	Prospective pilot study (n = 117), 12-month follow-up	Both IUS and copper IUD well tolerated, high satisfaction and compliance rates	[81]
Aslam *et al.* (2010)	Dysmenorrhea and HMB	Consecutive case series of 48 adolescents with HMB and dysmenorrhea resistant to oral treatment	93% improvement	[82]
Pillai *et al.* (2010)		Retrospective study, adolescent with menstrual problems and various medical disorders	LNG-IUS significant therapeutic benefit for 12 out of 14 patients aged 11–21 years	[83]
Paterson *et al.* (2009)	HMB and contraception	Cohort n = 179 (73% nulliparous)	Most common indications for use are HMB, contraception or both, followed by endometriosis and dysmenorrhea. 1-year continuation rate; 85% cumulative expulsion incidence 8%	[84]
Godfrey *et al.* (2010)	Compliance	Randomized, pilot study in adolescents (n = 23) LNG-IUS vs copper IUD	Continuation rates at 6 months, LNG-IUS 75% vs copper IUD 45% users	[85]
Behringer *et al.* (2011)	Compliance	Retrospective cohort study (n = 828), 104 (12.6%) nulliparous women, of which 131 (15.8%) were ≤20 years of age	Nulliparous women did not have more expulsions or removals because of dissatisfaction; this was not different to parous women (6.7 vs 11.5%; p = 0.15)	[86]

HMB: Heavy menstrual bleeding; IUS: Intrauterine system; LNG-IUS: Levonorgestrel-releasing intrauterine system.

Despite the evidence described above, the clinical practice seems to have remained unchanged at least in some settings. A survey among general practitioners from the UK showed that the LNG-IUS was not widely promoted or provided to young nulligravid women. Misconceptions relating to pelvic inflammatory disease and risk of ectopic pregnancy and perceived difficulty of insertion in nulligravidae were frequent [88]. Thus, education of healthcare professionals needs to be improved and local guidelines should be updated to encourage the use of the LNG-IUS in young nulliparous women. Encouragingly, planned postabortal use of the LNG-IUS has also increased among teenagers undergoing an induced abortion [89].

LNG-IUS in the treatment of HMB

The LNG-IUS is recognized as the most cost-effective nonsurgical method of treatment for HMB, and it has become the first-line recommendation for the treatment of HMB by several national and international guidelines, including the NICE guideline for HMB in the UK. However, a lot of research is still carried out in this indication, and the summary of the clinical trials published within the 5 last years is presented in Table 3 [90–93]. In brief, when compared with oral treatments either with cyclic medroxyprogesterone acetate or combined oral contraceptives [92], the LNG-IUS was superior in reducing menstrual bleeding and in improving blood hemoglobin levels among women suffering from documented menorrhagia.

In addition, two recent reviews have been published on the use of the LNG-IUS in the treatment of menorragia [91,94].

Pooled analysis of five randomized studies on the treatment of idiopathic menorrhagia concluded that the LNG-IUS is effective in reducing HMB and in increasing body iron stores as evidenced by increases in blood hemoglobin and ferritin levels [94]. The second, more extensive review including all available literature on the use of the LNG-IUS in women with HMB summarized that the LNG-IUS is superior to other medical treatments and comparable to endometrial resection in reducing HMB [92]. Moreover, the high efficacy of the LNG-IUS is seen over a variety of different countries and healthcare settings. Taken together, these reviews highlight the use of the LNG-IUS as the first-line treatment of HMB.

Table 3. Recently published articles on clinical studies on the use of levonorgestrel-releasing intrauterine system in treatment of heavy menstrual bleeding.

Study (year)	Methodology	Primary outcome measures	Results	Ref.
Kaunitz *et al.* (2010)	RCT: LNG-IUS vs oral MPA	MBL (hematin alkaline method)	LNG-IUS reduces menstrual blood loss more effectively and has a higher likelihood of treatment success than oral MPA	[90]
Kaunitz and Inki (2012)	RCT: LNG-IUS vs oral MPA	Hb and ferritin	Women treated with the LNG-IUS had greater increases in hemoglobin and ferritin levels than women treated with oral MPA	[91]
Shabaan *et al.* (2011)	RCT: LNG-IUS vs COC	Treatment failure rate, MBL (alkaline hematin and PBAC), Hb and ferritin	Treatment failure rate was lower and reduction of MBL greater with LNG-IUS, compared with COC. Hb and ferritin increased more in the LNG-IUS group	[92]
Chattopdhyay *et al.* (2011)	Prospective single-group trial	MBL	LNG-IUS reduced MBL significantly at all observation points (3–36 months) vs baseline value	[93]

COC: Combined oral contraceptive; Hb: Hemoglobin; LNG-IUS: Levonorgestrel-releasing intrauterine system; MBL: Menstrual blood loss; MPA: Medroxyprogesterone acetate; OC: Oral contraceptive; PBAC: Pictorial blood loss assessment chart; RCT: Randomized controlled trial.

Use of the LNG-IUS as part of HT for climacteric symptoms

The LNG-IUS is also suitable for endometrial protection during ET for climacteric symptoms. A 5-year-long clinical study in perimenopausal women transitioning from contraception to HT with the LNG-IUS reported on the bleeding pattern [95]. Adding ET was not associated with any increase in bleeding/spotting in LNG-IUS users, thus suggesting that it is a good strategy to transition from contraception to menopause. A systematic review and meta-analysis on the LNG-IUS plus ET concluded that the LNG-IUS was more effective than sequential medroxyprogesterone acetate and comparable with other systemic progestogen regimens for endometrial protection in perimenopausal and postmenopausal women taking ET [96]. Another systematic review came to a similar conclusion, stating that the LNG-IUS was at least as effective as other routes of progestin administration in HT [97].

Expert commentary

This overview confirms the high efficacy of LNG-IUS independent of the user, the cost–effectiveness of LNG-IUS used for contraception or for the treatment of HMB and the safety and acceptability when used on several indications. Postabortal insertion of the IUCD has been shown to be an effective means to avoid repeat terminations and should be promoted following both medical and surgical abortions. In women with several medical conditions, the LNG-IUS does not appear to have adverse effects on the course of the underlying disease even during long-term use.

Five-year view

As presented above, there is an increasing number of nulliparous women requiring effective contraception for longer. The development of a new IUS targeted for younger women has recently been initiated. A very recent publication focuses on the low-dose LNG contraceptive system (LCS) – a new LNG-releasing IUS developed for contraception. Two experimental IUSs with different LNG release rates (LCS 12 and LCS 16 with corresponding *in vitro* LNG release rates of 12 and 16 µg/day, respectively) that can be used for up to 3 years were compared with the currently marketed 20 µg LNG-IUS (Mirena). A potential advantage of a smaller IUS with a smaller insertion tube diameter may be easier and less painful placement, therefore, improving its acceptability and use in women with no previous vaginal delivery. In addition, IUSs with lower daily release rates of LNG lead to lower serum hormone levels, and may potentially reduce associated progestin-related adverse effects [98].

Another group, which is growing in numbers, is obese women. These women are not good candidates for estrogen-containing contraceptives, and the efficacy of systemically acting progestin-only contraceptives may be impaired. Frequently, obesity is associated with dysfunctional uterine bleeding, which may be worsened by use of a Cu-IUD. The limited evidence published to date suggests that the efficacy and safety profile of the LNG-IUS in obese women are similar to that observed in women with normal BMI. More research would be welcome in this group of women.

Recent studies have indicated that uptake of LARCs can be increased by proper counseling [73]. In the future, owing to their superior effectiveness in real-life use, cost–effectiveness and established safety profile, the LARCs are expected to become the contraceptive methods of first choice to women throughout their reproductive period.

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P Inki is employed by Bayer HealthCare Pharmaceuticals AG, manufacturer of the LNG-IUS. K Gemzell-Danielsson and O Heikinheimo serve occasionally on advisory boards or act as ad hoc invited speakers at scientific meetings for Bayer HealthCare Pharmaceuticals AG. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Use of the levonorgestrel-releasing intrauterine system (LNG-IUS) is increasing worldwide in several indications and in all age groups of women.
- The LNG-IUS is the most cost-effective nonsurgical treatment of heavy menstrual bleeding, it provides similar clinical outcomes compared with endometrial ablation and is a less invasive alternative to hysterectomy and allows fertility preservation.
- Postabortal insertion of the intrauterine contraceptive device (IUCD) has been shown to be an effective means to avoid repeat terminations. Insertion of IUCD should be performed as early as possible following abortion.
- In women with various pre-existing medical conditions (e.g., HIV infection, coagulopathies, obesity), the LNG-IUS does not appear to have adverse effects on the course of the underlying disease.
- The adverse effects of the LNG-IUS are established. Use of the LNG-IUS is not associated with an increased risk of arterial or venous thrombosis, nor with the risk of breast cancer in women of reproductive age. Uterine perforation is a rare complication which should be taken into account, in particular in breast-feeding women.
- The LNG-IUS for endometrial protection as part of hormone therapy for climacteric symptoms is at least as effective as other routes of progestin administration.
- Despite existing evidence on safety, in some settings, healthcare providers still have reservations about using IUCD for nulliparous women. Thus, providers would need to be educated and local guidelines updated according to the available recent information.
- In the future, long-acting reversible contraceptives are expected to become the contraceptive methods of first choice to women throughout their reproductive period owing to their superior effectiveness in real-life use, cost–effectiveness and established safety profile.

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