



Review

Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)—A systematic enquiry and overview

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Abstract

Levonorgestrel releasing-intrauterine systems (LNG-IUS) were originally developed as a method of contraception in the mid 1970s. The only LNG-IUS approved for general public use is the Mirena® LNG-IUS, which releases 20 mcg of levonorgestrel per day directly in to the uterine cavity. However, new lower dose (10 and 14 mcg per day) and smaller sized LNG-IUS (MLS, FibroPlant-LNG) are currently under clinical development and investigation. Research into the non-contraceptive uses of LNG-IUS is rapidly expanding. In the UK, LNG-IUS is licensed for use in menorrhagia and to provide endometrial protection to perimenopausal and postmenopausal women on estrogen replacement therapy. There is limited evidence to suggest that LNG-IUS may also be beneficial in women with endometriosis, adenomyosis, fibroids, endometrial hyperplasia and early stage endometrial cancer (where the patient is deemed unfit for primary surgical therapy). This systematic enquiry and overview evaluates the quality of evidence relating to the non-contraceptive therapeutic uses of LNG-IUS in gynaecology.

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Keywords: Levonorgestrel; Intrauterine devices; Medicated; Menorrhagia; Endometriosis; Estrogen replacement therapy; Endometrial hyperplasia; Progestogen; Therapy

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1. Introduction

The only levonorgestrel-releasing intrauterine system (LNG-IUS) approved for general public use is the Mirena[®] (Schering AG), which is a T-shaped plastic intrauterine device (IUD) that releases levonorgestrel (20 mcg per day) directly into the uterine cavity. The mean systemic levels of levonorgestrel with this LNG-IUS (425 pg/ml at 1 month, 330 pg/ml at 6 months, mean age of subjects was 31 years (range 18–42)) [1] are less than those achieved with therapeutic oral or parenteral doses of progestogens (hence minimizing systemic side effects) and exceeds the critical value of 200 pg/ml below which ovulation occurs [2]. Mirena was first launched in Finland in 1990 and has been marketed in the UK since 1995 as a contraceptive device. Two new lower levonorgestrel dose and smaller sized LNG-IUS devices are currently under clinical development and investigation: FibroPlant[™]-LNG (frameless device, Contrel Research, Belgium) and MLS system, releasing 14 and 10 mcg levonorgestrel per day, respectively [3,4].

Mirena[®] LNG-IUS is currently licensed in the UK as a 5-year contraceptive agent (license awarded 1995), treatment for idiopathic menorrhagia (license awarded 2001), and to provide uterine protection during estrogen replacement therapy in perimenopausal and postmenopausal women (license awarded 2005). The latter two applications for Mirena[®] LNG-IUS are not licensed in USA or Canada.

The fertility control provided by LNG-IUS is comparable with that of female sterilisation, and is completely reversible [5]. There are many other non-contraceptive beneficial effects of LNG-IUS that have important public health implications. These have been summarised by several reviews [6–9] and policy statements [10], and incorporated within one systematic review examining all types of intrauterine device [11]. However, there has since been a considerable expansion of publications in this area, many of which have contrasting methodological quality and results. This article expands on past reviews by incorporating these recent advances and performs an up-to-date systematic review focused entirely on LNG-IUS. Furthermore, this review evaluates the quality of supporting evidence, and where available, presents information relating to adverse effects, cost-effectiveness and health related quality of life (HRQL) issues.

2. Materials and methods

All observational and experimental studies examining the use of LNG-IUS in gynaecology were retrieved from MEDLINE (1996–2005), EMBASE (1996–2005 week 08), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), The National Research Register NRR (<http://www.update-software.com/national/>), Medical Research Council's Clinical Trials Register and

details on reviews in progress collected by the NHS Centre for Reviews and Dissemination were searched. Schering HealthCare (UK) were also contacted for further information on licensing and any unpublished controlled clinical trials.

The following search terms and word variants were used: 'exp Intrauterine Devices, Medicated/', 'levonorgestrel releasing', 'levonorgestrel-releasing', 'LNG-IUS', 'LN-IUS', 'LN-IUD', 'LNG-IUD', 'mirena.tw.' 'Levonorgestrel adj5 (intrauterine or device or coil or system). tw', 'progest\$ adj5 (intrauterine or device or coil or system).tw', 'intra-uterine progestogen' combined with "AND" to 'gyne\$', 'therapy' 'endometriosis', 'endometrio\$.mp', 'genital neoplasms, female', 'dysmenorrhoea', 'pelvic pain', 'estrogen replacement therapy', 'hormone replacement therapy' or 'genital diseases, female'. In addition, the citation lists of relevant publications, review articles, abstracts of scientific meetings and included studies will also be searched. The search was completed March 2005. Obtained data were qualitatively and quantitatively analysed. If trials are deemed suitable (similar population groups, trial methodology and outcome measures) meta-analysis will be performed.

3. Results

A summary of the studies identified describing the non-contraceptive therapeutic use of LNG-IUS according to the therapeutic indication is shown in Table 1. The associated level of evidence and strength of recommendation for each indication is also indicated according to accepted criteria [12].

3.1. Menorrhagia

Early RCTs and cohort studies evaluating the contraceptive efficacy of LNG-IUS against Cu-IUCD showed women who received LNG-IUS reported less dysmenorrhoea and menstrual blood loss (MBL) [35,36]. This provided a basis to examine whether LNG-IUS would also decrease menstrual blood loss in women with idiopathic menorrhagia (dysfunctional uterine bleeding, DUB) and compare its efficacy against established medical and surgical treatments for menorrhagia. In total, approximately 670 women with menorrhagia have used LNG-IUS as part of a comparative or non-comparative study (listed in Table 2) evaluating the efficacy of LNG-IUS in treating menorrhagia. Women using the frameless FibroPlant-LNG[™] or Femilstrade LNG-IUS (20 mcg/24 h) devices for contraception [33,37] or treatment of menorrhagia [30–33] also reported decreased MBL, however study sample sizes were limited ($n = 76$ menorrhagia cases) and the devices remain under clinical development.

Two incomplete trials were identified in the search, Satisfaction with Mirena and Ablation: a Randomised Trial (SMART) [38] and Thermo-Ablation versus the

Table 1

Summary of studies that assess LNG-IUS use in various non-contraceptive therapeutic indications as primary study outcome measures

Therapeutic use of LNG-IUS	RCTs		Cohort studies	Prospective or retrospective observational studies	Case report or small case series	Level of evidence	Strength of recommendation
	More than 50 women in LNG-IUS arm of trial	Less than 50 women in LNG-IUS arm of trial					
Menorrhagia	1	9	2	5	0	I, II, III	A
Fibroids/fibroid related menorrhagia	1 ^a	2 ^a	1	6	1	II, III	B
Endometriosis	0	2	0	3	0	I, III	C
Adenomyosis	1	0	0	1	1	I, III, III	C
Uterine protection with estrogen replacement therapy in perimenopausal and postmenopausal women	3	4	3	7	0	I, II, III	A
Uterine protection with tamoxifen in postmenopausal women	1	0	0	1	0	I, III	A
Endometrial hyperplasia	0	0	1	3	2	II, III	C

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

^a Trial(s) exist, but therapeutic outcome was not assessed as a priori primary outcome measure in the RCT comparison.

Classification of evidence levels

- (Ia) Evidence obtained from meta-analysis of randomised controlled trials.
- (Ib) Evidence obtained from at least one randomised controlled trial.
- (IIa) Evidence obtained from at least one well-designed controlled study without randomisation.
- (IIb) Evidence obtained from at least one other type of well-designed quasi-experimental study.
- (III) Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- (IV) Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Strength of recommendation

- (A) Directly based on category I evidence.
- (B) Directly based on category II evidence or extrapolated recommendation from category I evidence.
- (C) Directly based on category III evidence or extrapolated recommendation from category I or II evidence.
- (D) Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.

Table 2
LNG-IUS studies assessing therapeutic effect in women with menorrhagia

Authors	Year of publication	Study type	Sample size of women with menorrhagia	Comparison	Outcomes (within 1-year follow up unless stated otherwise)
Hurskainen et al. [13,14]	2001, 2004	RCT	236	119 LNG-IUS vs. 117 hysterectomy For the LNG-IUS group: at 1 year 81/119 and at 5 year 57/119 continued to have LNG-IUS in situ	5-Year follow up: Of the LNG-IUS group by 1 year 68% continued with LNG-IUS and 20% had TAH Both treatments had comparable improvements in HRQL
Soysal et al. [15]	2002	RCT	72	36 LNG-IUS vs. 36 thermal balloon ablation 14% Drop out from LNG-IUS	Greater reductions in PBAC with ablation than LNG-IUS Comparable improvements in haemoglobin; ablation group perceived greater improved HRQL than LNG-IUS
Crosignani et al. [16]	1997	RCT	70	35 LNG-IUS vs. 35 TCRE 14% Drop out from LNG-IUS	Marginally greater reductions in PBAC with TCRE Comparable satisfaction rates
Kittelsen [17]	1998	RCT	60	30 LNG-IUS vs. 30 TCRE 12% Drop out rate	Comparable reductions in PBAC Comparable satisfaction rates
Istre and Trolle [18], Rauramo et al. [19]	2001, 2004	RCT	59	30 LNG-IUS vs. 29 TCRE 31% Drop out rate	3-Year follow up: Greater reductions in PBAC with TCRE than LNG-IUS (90% cure vs. 67% cure) at 1 year, but comparable reductions of MBL noted at 3 years Increased haemoglobin and ferritin with both treatments
Lahteenmaki et al. [20]	1998	RCT	56	28 LNG-IUS vs. 28 medical treatment whilst awaiting hysterectomy 25% Drop out from LNG-IUS	At 6 m, 64% LNG-IUS cancelled TAH whilst 14% cancelled TAH in medical treatment group
Reid and Virtanen-Kari [21]	2005	RCT	51	25 LNG-IUS vs. 26 mefenamic acid 16% Drop out from LNG-IUS	Greater reductions in MBL, PBAC and total menstrual fluid loss with LNG-IUS (90% vs. 23%) at 6 months
Barrington et al. [22]	2003	RCT	50	25 LNG-IUS vs. 23 balloon ablation 12% Drop out rate	Comparable reductions in PBAC
Irvine et al. [23]	1998	RCT	44	22 LNG-IUS vs. 22 oral norethisterone No drop out rate	Comparable reductions in MBL (>90%); greater satisfaction with LNG-IUS
Milsom et al. [24]	1991	RCT	35	20 LNG-IUS vs. 15 tranexamic acid 20% Drop out from LNG-IUS	Greater reduction in MBL with LNG-IUS (>90%)

Romer [25]	2000	Prospective cohort	30	LNG-IUS vs. roller ball endometrial ablation	Comparable reductions in MBL and rates of amenorrhoea
Henshaw et al. [26]	2002	Retrospective cohort	62	LNG-IUS vs. microwave endometrial ablation	Mean 14-month follow up: Comparable reductions in MBL and dysmenorrhoea Comparable patient satisfaction rates
Mansour and Mansour [27]	1998	Prospective	52	No comparison LNG-IUS	91% of Women had improved dysmenorrhoea and menorrhagia 83% Continued with treatment beyond 1 year
Barrington and Bowen-Simpkins [28]	1997	Prospective	50	LNG-IUS No comparison Women were awaiting TCRE or hysterectomy	Reduced PBAC in 82% 8% Amenorrhoea No change in haemoglobin or ferritin Decreased premenstrual symptoms in 56% Reduced dysmenorrhoea in 80%
Monteiro et al. [29]	2002	Prospective	44	LNG-IUS No comparison	Decreased MBL and increased haemoglobin 80% Continuation rate at 1 year
Wildemeersch [30–32]	2004	Prospective	12 in 2004, 32 in 2001	No comparison FibroPlant-LNG	Decreased PBAC (median MBL decreased by 90%) Decreased dysmenorrhoea
Wildemeersch and Rowe [33]	2005	Prospective	60 Women: 28 normal periods, 32 menorrhagia	No comparison Femilstrade LNG-IUS 20 mcg/24 hr	Similar reductions in MBL (96–99%) for both groups 33% Developed amenorrhoea (10 women in each group)
Xiao et al. [34]	2003	Prospective	34	LNG-IUS No comparison	3-Year follow up: Decreased MBL at 1 year (84%) and 3 years (85%) 33% Amenorrhoea at 6 months Increased hemoglobin and serum ferritin

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

- FibroPlant-LNG is a frameless low-dose (releasing 14 mcg levonorgestrel/day) frameless LNG-IUS.
- HRQL, health related quality of life assessments.
- LNG-IUS releasing 20 mcg levonorgestrel/day.
- MBL, menstrual blood loss.
- PBAC, pictorial blood loss assessment chart.
- TCRE, transcervical endometrial resection.

Levonorgestrel Intrauterine System (TALIS) [39]. Furthermore, our unit is about to commence the ECLIPSE trial (Effectiveness and Cost-effectiveness of Levonorgestrel containing Intrauterine system in Primary care against Standard treatment, ISRCTN 86566246) in the UK.

Overall, for all listed studies, LNG-IUS use in women with menorrhagia reduces menstrual blood loss by 79–97%. No RCTs have compared LNG-IUS with placebo or no treatment in women with menorrhagia. Importantly, studies have used various outcome measures, which precludes pooled meta-analysis. These include: indirect (pictorial blood loss assessment chart, PBAC) or direct (alkaline haematin method) measures of MBL; patient willingness to continue with treatment; or patient preference to abandon LNG-IUS treatment in favour of hysterectomy or endometrial resection. There are insufficient participants to show long-term therapeutic effect with LNG-IUS, as most studies did not extend beyond 1-year follow up. The total number of participants continuing with LNG-IUS by 3-year [19,34] and 5-year follow up [14] was 96 cases.

Of the 10 trials depicted in Table 2, seven [13,16–18,20,23,24] have been incorporated in two Cochrane reviews [40,41] and one systematic review [42]. Three recent RCTs [15,21,22] and two quality cohort studies [25,26] not included in the prior published meta-analyses have also been listed in Table 2. The high patient satisfaction (72–94%) and overall continuation rates (65–88%) obtained in these RCTs are consistent with those found in other observational and questionnaire based studies examining LNG-IUS use in women with menorrhagia [29,43,44].

Interpreting the evidence from Table 2, LNG-IUS system is at least comparable or more effective than oral progestogens. Similar rates of patient satisfaction and quality of life are reported when comparing LNG-IUS against transcervical endometrial resection or balloon ablation. However, surgical methods are significantly more effective in reducing menstrual bleeding or inducing amenorrhoea within 1-year follow up. However, one trial with longer follow up of 3 years [19] showed no significant difference between the LNG-IUS and TCRE in the reduction of menstrual blood loss.

Meta-analyses and RCTs have shown that a significant proportion of women with menorrhagia initially treated with either conservative surgery [45] or LNG-IUS [42] are likely to require hysterectomy as a definitive treatment. However, an RCT ($n = 236$) with 5-year follow up has shown hysterectomy does not improve overall health related quality of life significantly more than LNG-IUS and it can cause serious complications [14]. Furthermore, the same trial showed that LNG-IUS was more cost-effective than hysterectomy at 1-year [13] (US\$ 1530 versus US\$ 4222) and 5-year [14] follow up (US\$ 2817 per participant versus US\$ 4660 per participant). This estimate includes the direct (e.g. operative, costs) and indirect costs (e.g. sick leave days) associated with the 42% of the women assigned to the LNG-IUS group who eventually underwent hysterectomy.

Menorrhagia may arise from inherited bleeding disorders (e.g. von Willebrand's Disease, factor XI deficiency, Hermansky-Pudlak syndrome). A prospective study ($n = 16$) has shown reduction in menstrual blood loss, improvement in quality of life in all women with menorrhagia due to a known inherited bleeding disorder when treated with LNG-IUS [46].

3.2. Uterine fibroids and fibroid related menorrhagia

One cohort study, five prospective observational studies and one case report have directly assessed the use of LNG-IUS in treating fibroids and fibroid related menorrhagia or dysmenorrhoea. Three RCTs, undertaken for other indications, have described decreased incidence of fibroids following LNG-IUS insertion [35,54,55]. The features of these studies are shown in Table 3. Apart from one study [35], study duration and follow up did not exceed 1 year. Inclusion criteria were clearly stated in two studies: women with fibroid uterus below 12 weeks gestational size on pelvic examination or 380 ml uterine volume on pelvic ultrasound [47,48].

All studies directly assessing LNG-IUS in women with fibroids reported decreased menstrual blood loss (84–90%) and similar increases in haemoglobin of 2–3 g/dl [47,48,51]. However, there was inconsistency on whether LNG-IUS is associated with decreased fibroid size [48,52,53] or no change in fibroid size [50,51,55]. Fibroid size following LNG-IUS was not assessed in one cohort study [47].

Regarding the indirect studies, one large RCT suggested there may be decreased incidence of uterine fibroids with LNG-IUS compared to Cu-IUCD [35]. A similar observation of 13% decreased incidence of fibroids was observed in a RCT comparing LNG-IUS and tamoxifen against tamoxifen alone [54].

3.3. Endometriosis

Two RCTs and three prospective observational studies were identified. All studies had limited sample sizes (range 11–39 participants in LNG-IUS arm of study), and their features are shown in Table 4. Population groups differed considerably between studies and included women with early stage and late stage endometriosis, rectovaginal endometriosis, immediately surgically treated endometriosis, prior history of endometriosis diagnosis, chronic pelvic pain and/or dysmenorrhoea. This heterogeneity of population, combined with small sample size, limits the strength and validity of the findings. Two studies from the same group [57,60] report approximately 40% absolute risk reduction in dysmenorrhoea by 1 year with LNG-IUS use. This is consistent with a 3-year prospective study [59] and a 1-year RCT [56] that reported similar magnitude reductions in dysmenorrhoea and chronic pelvic pain. A prospective study reported decreasing severity of endometriosis on AFS staging following LNG-IUS insertion [58].

Table 3
LNG-IUS studies directly or indirectly assessing therapeutic effect on fibroids or fibroid related menorrhagia

Authors	Year of publication	Study type	Sample size	Comparison	Outcomes (within 1-year follow up unless stated otherwise)
Direct studies					
Soysal and Soysal [47]	2005	Prospective and retrospective cohort	64	32 LNG-IUS vs. 32 thermal balloon ablation (historical matched group)	Comparable effective reductions in PBAC (around 90%) Comparable increases in haemoglobin Fibroid size change not assessed
Grigorieva et al. [48]	2003	Prospective and retrospective	67	No comparison	Effective reductions in PBAC Improved ferritin and haemoglobin 40% Amenorrhoea at 12 months Decrease in fibroid size (33%)
Mercorio et al. [49]	2003	Prospective	19	No comparison	Reduced PBAC, but 14/19 still had persistent menorrhagia
Wildemeersch and Schacht [50]	2002	Prospective	14	No comparison FibroPlant-LNG	Reduction in MBL in 13/14 No reduction in fibroid size
Starczewski and Iwanicki [51]	2000	Prospective	12	No comparison	Reduction in MBL 11/12 cases Amenorrhoea 50% cases Improved haemoglobin No change in fibroid size
Singer and Ikomi [52]	1994	Prospective	5	No comparison	Reduction in MBL Reduction in fibroid size Follow up to 18 months
Fong and Singh [53]	1999	Case report	1	No comparison	Reduction in MBL and fibroid size
Indirect studies					
Gardner et al. [54]	2000	RCT	122	64 LNG-IUS and tamoxifen against 58 tamoxifen 27% Drop out rate from LNG-IUS group	13% Reduction in fibroids from baseline in LNG-IUS group
Inki et al. [55]	2002	Prospective study (examine one arm of RCT)	38	117 had LNG-IUS for menorrhagia, of this 38/119 (32%) had uterine fibroids	No ultrasonographic change in uterine fibroids, but decreased endometrial thickness Increased risk of ovarian cysts compared to hysterectomy
Sivin and Stern [35]	1994	RCT	2226 Recruited, 1125 had LNG-IUS 1121 had Cu-IUCD	LNG-IUS vs. Cu-IUCD (TCu 380 Ag) Parous women aged 18–38, all desiring contraception	7-Year follow up: LNG-IUS compared to Cu-IUCD has decreased incidence of dysmenorrhoea, vaginitis, fibroids, but higher rates of amenorrhoea, follicular ovarian cysts, acne, mastalgia, weight gain, and headache

Table 3 (Continued)

Authors	Year of publication	Study type	Sample size	Comparison	Outcomes (within 1-year follow up unless stated otherwise)
			Baseline fibroid incidence: unclear Identified 15 fibroids at end of study	7 Year study follow up (3416 women years in LNG-IUS and 3975 women years in Cu-IUCD) 11.4% Drop out rate from LNG-IUS	LNG-IUS: 50% amenorrhoea or oligomenorrhoea by end of study, compared to 9% with Cu-IUCD

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

3.4. Adenomyosis

One non-blinded RCT ($n = 95$), one prospective observational study and one case report were identified. The features of the studies are listed in Table 5. All studies showed a reduction in adenomyosis related dysmenorrhoea and menorrhagia, and this effect was statistically significant in the RCT [62] that compared LNG-IUS against expectant treatment in women following TCRE for adenomyosis. However, dysmenorrhoea and menorrhagia observed in the trial may not necessarily be due to adenomyosis.

3.5. Endometrial protection during estrogen replacement therapy or tamoxifen in peri-menopausal women

Seven RCTs, three cohort studies and seven observational studies have described the use of LNG-IUS to protect the endometrium from endometrial hyperplasia or malignant transformation during exogenous estrogen replacement therapy (ERT) in perimenopausal and postmenopausal women. One RCT [54] and one observational study ($n = 6$) [65] have examined the endometrial protective effect of LNG-IUS during tamoxifen therapy in postmenopausal women. The characteristics of these studies are summarised in Table 6. The tamoxifen RCT [54] showed that 91% women had endometrial suppression (histological decidual or atrophic response) in the LNG-IUS and tamoxifen group ($n = 47$) compared to 75% in the tamoxifen only group ($n = 52$) [54].

RCTs differed in population subgroups (perimenopausal and postmenopausal women), methods of ERT administration (such as implant, oral, transdermal gel, vaginal ring) comparisons (cyclic oral estrogen/progestogen HRT, continuous combined estrogen/progestogen HRT, vaginal progestogen, subdermal progestogen, low dose LNG-IUS [10 or 14 mcg systems] versus higher does LNG-IUS [20 mcg]) and methods of assessing endometrial suppression outcome (clinical, histological, ultrasonographic, MRI). A meta-analysis of discrete groups of studies may be less informative than individually listing the study design and outcomes, and was therefore not performed.

Endometrial suppression and symptomatic improvement of menopausal symptoms (e.g. hot flushes) was achieved in all studies examining LNG-IUS use in women receiving ERT. From the study outcomes, amenorrhoea appeared to be more common in postmenopausal women receiving LNG-IUS (studies ranging from 61% to 100% of subjects) than peri-menopausal women (studies ranging from 38% to 83% of subjects), although this was not formally statistically tested due to study heterogeneity.

Seven studies have reported follow up beyond 1 year [66,75,78–83], three reported up to a maximum of 5 years [75,79,80] and one study published its interim 1-year results from a proposed 3-year study duration [3]. There was no statistically significant difference between LNG-IUS 10 mcg and LNG-IUS 5 mcg in one RCT ($n = 108$) [67].

Table 4
LNG-IUS studies assessing therapeutic effect in women with endometriosis

Author	Year of publication	Study type	Sample size	Comparison	Outcomes (within 1-year follow up unless stated otherwise)
Petta et al. [56]	2005	RCT	82 With endometriosis, dysmenorrhoea and chronic pelvic pain	39 LNG-IUS vs. 43 GnRH analogue	6 Months follow up: Comparable reductions in pelvic pain and improved quality of life measures Greater amenorrhoea with GnRH than LNG-IUS (98% vs. 70%)
Vercellini et al. [57]	2003	RCT	40 Parous women, not desiring fertility, with endometriosis associated dysmenorrhoea and receiving conservative surgical treatment of endometriosis	20 Post-operative LNG-IUS and endometriotic surgery vs. 20 endometriotic surgery alone 10% Drop out from LNG-IUS group	Decreased recurrence of dysmenorrhoea in LNG-IUS vs. surgery alone group (10% vs. 45%, $p = 0.03$) 28% or 50% LNG-IUS users had amenorrhoea or oligoamenorrhoea Comparable levels of patient satisfaction (75% and 50%)
Lockhat et al. [58,59]	2004, 2005	Prospective	34 With symptomatic mild–moderate endometriosis	No comparison (1-year and 3-year follow up)	Decreased dysmenorrhoea and/or non-cyclical pelvic pain and AFS staging of endometriosis 68% Continuation rate at 1 year 56% Continuation rate at 3 years
Vercellini et al. [60]	1999	Prospective	18 Parous women who had history of previous endometriotic surgery and had recurrent dysmenorrhoea	No comparison	Amenorrhoea in 24% Oligoamenorrhoea in 47% Decreased dysmenorrhoea by 45% Decreased menstrual blood loss by 76% 75% Satisfaction rates
Fedele et al. [61]	2001	Prospective	11 Symptomatic women with rectovaginal endometriosis	No comparison	Decreased pelvic pain, dyspareunia, dysmenorrhoea related to endometriosis Decreased size of endometriosis lesions (ultrasound)

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

Table 5
LNG-IUS studies assessing therapeutic effect in women with adenomyosis

Authors	Year of publication	Study type	Sample size	Comparison	Outcomes within 1-year follow up
Maia et al. [62]	2003	RCT non-blinded	95 Women post TCRE for adenomyosis	53 LNG-IUS vs. 42 expectant	19% Of expectant group needed second treatment for uterine bleeding and pain compared to none in LNG-IUS Significantly lower rate of dysmenorrhoea in LNG-IUS (10%) than expectant (80%) group Significantly higher rate of amenorrhoea in LNG-IUS group (100% vs. 9%) at 1 year
Fedele et al. [63]	1997	Prospective	25 With adenomyosis related menorrhagia	No comparison	For all cases, reduction in PBAC, dysmenorrhoea
Fong and Singh [64]	1999	Case report	1 Enlarged adenomyosis uterus	No comparison	Improved haemoglobin and ferritin Reduction in uterine size, dysmenorrhoea, MBL

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

Participants in three separate publications [78,81,83] are likely to be from the same study cohort.

3.6. Endometrial hyperplasia

No RCTs were identified. Characteristics of the one cohort, three prospective observational studies, and two case reports/case series are shown in Table 7. Most studies examined women with non-atypical endometrial hyperplasia, but three studies have included women with atypical hyperplasia [86,87,89]. Hyperplasia of all types was regressed in all cases treated with LNG-IUS.

3.7. Endometrial cancer

The preferred primary treatment for early stage endometrial cancer is surgical hysterectomy, with systemic progestins used palliatively or as adjuvant treatments for higher stage cancers. A literature review of limited sized case series and cohort studies ($n = 81$ cases, 27 articles) has shown safe and effective treatment (overall 76% cure) with systemic progestin therapy in women with well differentiated stage 1 endometrial cancer [90].

This evidence, although limited in quality, establishes a plausible role for LNG-IUS in early stage disease, particularly in those women medically unfit for surgical therapy. One case report describes successful reversion of the cancer on endometrial biopsy when using a combination of oral progestogens and LNG-IUS in such an indication [91]. However, another case series (two patients) showed no regression of the endometrial cancer when treated with LNG-IUS alone in patients awaiting definitive surgical treatment [89]. A comparative study performed in 14 women with early stage endometrial cancer considered high risk for surgery showed successful reversion of cancer on endometrial biopsy in 75% of cases at 12 months [92].

However, a case series has identified two cases of endometrial carcinoma that were diagnosed following insertion of LNG-IUS [93]. Clearly, further cases, controlled trials, and longer follow up are required in order to obtain more valid conclusions.

3.8. Dysmenorrhoea and pain

Only one observational study has formally examined the therapeutic use of LNG-IUS in women with primary and secondary dysmenorrhoea [32]. The study is of poor quality (limited sample size, $n = 18$ and non-comparative) which makes interpretation of the observed beneficial response difficult. However, reductions in dysmenorrhoea have been reported in numerous LNG-IUS trials [26,35,94–97] and observational studies [28,98,99], albeit not being an a priori primary outcome measure in the vast majority.

An RCT ($n = 236$) that compared LNG-IUS with hysterectomy for women with menorrhagia evaluated pain

Table 6
LNG-IUS studies assessing use to provide uterine protection during estrogen replacement or tamoxifen therapy

Authors	Year of publication	Study type	Sample size	Comparison group	Outcomes (within 1 year of follow up unless stated otherwise)
Tamoxifen studies					
Gardner et al. [54]	2000	RCT	Initial recruitment of 122 Postmenopausal breast cancer women	64 LNG-IUS and tamoxifen group vs. 58 tamoxifen group only 27% Drop out rate from LNG-IUS arm	All LNG-IUS had endometrial suppression (histological decidual response) Decreased endometrial polyps and submucous fibroids in LNG-IUS group
Turnbull et al. [65]	1998	Prospective	6 Postmenopausal breast cancer women with irregular thickened endometrium on tamoxifen therapy	No comparison Inserted LNG-IUS	No change in endometrial thickness with TV ultrasound A reduction in sub-endometrial cysts and endometrial volume with MRI by 6 months
Estrogen replacement studies					
Boon et al. [66]	2003	RCT	200 Perimenopausal women	100 LNG-IUS and 100 oral estradiol vs. cyclic/combined oral estrogen and progestogen HRT (Trisequens) 18% Drop out rate from LNG-IUS group	2-Year follow up: Endometrial suppression (atrophic or inactive) greater with LNG-IUS than oral HRT: 100% vs. 6% LNG-IUS: initial erratic bleeding, 62% amenorrhoeic by 2 years Cyclic HRT: normal regular monthly bleeds in 70–80%
Wolter-Svensson et al. [67]	1997	RCT	112 Perimenopausal women symptomatic of menopause	51 LNG-IUS 10 mcg/24 h plus estrogen (oral/transdermal) vs. 45 LNG-IUS 5 mcg/24 h plus estrogen (oral/transdermal) 11% Drop out rate	95/96 Cases had histological endometrial suppression Amenorrhoea in most cases (62% for 5 mcg and 61% for 10 mcg groups) Satisfactory relief of menopausal vasomotor symptoms
Raudaskoski et al. [68]	2002	RCT	163 Postmenopausal women Oral estrogen with: 54 10 mcg/24 h LNG-IUS (MLS) or 56 20 mcg/24 h LNG-IUS or 53 oral progestogen	Different progestogen formulations of HRT combining oral estradiol with high or low dose LNG-IUS or cyclical oral progestogen 7% Drop out from combined LNG-IUS 10 and 20 mcg groups	Endometrial suppression (histologically) and amenorrhoea in >98% of LNG-IUS cases Proliferative endometrium and regular withdrawal bleeds with oral progestogen
Raudaskoski et al. [69]	1995	RCT	40 Postmenopausal	20 LNG-IUS plus transdermal estrogen vs. 20 continuous oral estrogen and progestogen	Comparable endometrial suppression (histological and ultrasound)

Table 6 (Continued)

Authors	Year of publication	Study type	Sample size	Comparison group	Outcomes (within 1 year of follow up unless stated otherwise)
Andersson et al. [70]	1992	RCT	40 Perimenopausal	12% Drop out from LNG-IUS group 20 LNG-IUS and oral estrogen vs. 20 cyclic HRT (oral estrogen 3 weeks, oral progestogen 1 week)	Comparable improvement of menopausal symptoms 83% of LNG-IUS became amenorrhoeic, but cyclic HRT had regular withdrawal bleeds Both groups had endometrial suppression
Suhonen et al. [71]	1995	RCT	36 Postmenopausal	16 LNG-IUS and one subdermal estrogen implant vs. 20 LNG-IUS and three subdermal estrogen implants	Endometrial suppression in all cases 72% had amenorrhoea or spotting by 3 months
Suhonen et al. [72]	1995	RCT	19 Postmenopausal	No drop out reported 10 Oral estrogen and LNG-IUS vs. 9 oral estrogen and subdermal levonorgestrel-releasing implant No drop out reported	Comparable endometrial suppression
Suvanto-Luukkonen et al. [73–75]	1997, 1998, 1999	Prospective cohort	60 Postmenopausal women 20 Received LNG-IUS 21 Oral progesterone 19 Vaginal progesterone	All received transdermal estrogen gel 25% Drop out rate of LNG-IUS group at 5 years	5-Year follow up for 20 cases in LNG-IUS group: At 1 year varying degrees of amenorrhoea: 80%, LNG-IUS; 67%, oral progesterone; 53% in the vaginal progesterone At 5 years 80% amenorrhoea in LNG-IUS Endometrial suppression (histological, ultrasound) in all LNG-IUS cases
Antoniou et al. [76]	1997	Prospective cohort	56 Postmenopausal women with urogenital symptoms	28 Women with LNG-IUS plus daily transdermal estrogen vs. 28 women with estradiol-releasing vaginal ring plus vaginal progesterone	Comparable endometrial suppression (ultrasound)
Kalogirou [77]	1996	Prospective cohort	56 Postmenopausal	LNG-IUS and transdermal estrogen vs. estrogen releasing vaginal ring and oral progestogen	Comparable endometrial suppression (ultrasound and histological)
Sturdee et al. [3]	2004	Prospective	294 Postmenopausal	No comparison LNG-IUS 10 mcg/24 h (MLS device) and transdermal estrogen	Interim 1-year results from 3-year study: 67% Amenorrhoeic at 1 year; 9/294 Discontinued because of bleeding
Wildemeersch et al. [78]	2003	Prospective	83 Perimenopausal and 58 postmenopausal	No comparison	Up to 3-year follow up:

			* Mixed group of women-contraception needs, menorrhagia, vasomotor symptoms, fibroids	Used FibroPlant-LNG with transdermal estrogen gel	All effective endometrial suppression (ultrasound) 64% Amenorrhoea in perimenopausal group and 100% in postmenopausal group 5 Cases of fibroid related menorrhagia improved
Hampton et al. [79]	2005	Prospective	82 Perimenopausal	No comparison Use LNG-IUS with oral estrogen	5-Year follow up: 96–98% Non-proliferative endometrium 55% Amenorrhoea at 1 year 93% Amenorrhoea by fifth year 80 Per 100 women continuation rate at 5 years
Varila et al. [80]	2001	Prospective	40 Postmenopausal	No comparison Used LNG-IUS with oral or transdermal estrogen	5-Year follow up: 39 Completed 12 mths 29 Completed 5 years All cases had endometrial suppression (histological and ultrasound) 51% Amenorrhoea or only spotting at 5 years
Wildemeersch and Schacht [81]	2000	Prospective	22 Perimenopausal, 8 postmenopausal	19 Cases had FibroPlant LNG 14 mcg/24 h and 11 cases had 10 mcg/24 h doses All with transdermal estrogen gel	Up to 2.5 years follow up: All effective endometrial suppression (ultrasound) 77% Amenorrhoea in perimenopausal group and 100% in postmenopausal group
Suhonen et al. [82]	1997	Prospective	29 Perimenopausal and postmenopausal women	No comparison LNG-IUS and transdermal/subdermal/oral estrogen	3-Year follow up: All cases had endometrial suppression (ultrasound, histology) 79% Amenorrhoea at 3 years
Wildemeersch et al. [83]	2004	Prospective	24 Postmenopausal women	No comparison Used FibroPlant-LNG with oral estradiol or estrogen patches	3-Year follow up: All effective endometrial suppression (histologically and ultrasound) and clinical amenorrhoea

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

FibroPlant-LNG is a frameless low-dose LNG-IUS (releasing 14 mcg levonorgestrel/day). MLS is a low dose smaller sized LNG-IUS (releasing 10 mcg levonorgestrel/day).

Table 7
LNG-IUS studies assessing therapeutic effect in women with endometrial hyperplasia

Authors	Year of publication	Study type	Sample size	Comparison	Outcomes within 1-year follow up
Verside et al. [84]	2003	Retrospective cohort	57 Endometrial hyperplasia	LNG-IUS vs. oral progestogen	Greater regression with LNG-IUS that with oral progestogens (100% vs. 55%) at 3 months
Scarselli et al. [85]	1988	Prospective	31 (4 Atypical types)	No comparison	Endometrial regression in all cases
Perino et al. [86]	1987	Prospective	14 (1 Case atypical type)	No comparison	Endometrial regression in 29/31 cases at 16 months follow up
Wildemeersch and Dhont [87]	2003	Prospective	12 (Non-atypical and atypical types)	No comparison	Endometrial regression in all cases by 3 years
Rose and Edmonds [88]	2001	Case report	1	No comparison	Endometrial regression
Bahamondes et al. [89]	2003	Case report	1	No comparison	Endometrial regression

For all studies listed in table, we have reported the sample sizes originally recruited by the studies. Where the study drop out rate exceeds 10% we have stated this rate to provide the reader with an impression of the number of subjects actually evaluated by the study where this drop out rate is exceeded.

as an outcome using a RAND-36 health survey [13,14]. The trial showed greater pain in improvement in the hysterectomy group than LNG-IUS at 1 year. However, by 5 years, both LNG-IUS and hysterectomy groups had achieved almost identical reductions in pain.

Most studies have failed to distinguish dysmenorrhoea from co-existent pelvic pain disorders (e.g. endometriosis, chronic pelvic pain, chronic pelvic inflammatory disease) in their subgroup analyses. This may cause confounding. However, the fact the association is reproducible in so many studies suggests the effect is real even though the magnitude cannot be accurately ascertained.

3.9. LNG-IUS and effect on pelvic inflammatory disease

No RCTs have examined whether the incidence of pelvic inflammatory disease (PID) is modified following introduction of LNG-IUS as a primary outcome measure. One RCT [100] and reviews of the early LNG-IUS trials [101,102] has suggested a lowering of PID rates when using LNG-IUS compared to Cu-IUCD. Whereas, two early RCTs [35,103], a recent 5-year study [104] and a systematic review [105] of all the contraceptive trials have shown comparable rates of PID during the use of the LNG-IUS or a copper IUD.

3.10. Other non-contraceptive therapeutic indications

Large multicentre studies have not detected differences in cervical cytology or breast cancer incidence between copper IUD and LNG-IUS users, and non-users [35,101,102]. Long-term epidemiological studies are needed to confirm this finding, and whether these may represent alternative therapeutic indications.

3.11. Adverse effects

Irrespective of study design and indication all studies have reported adverse side effects following insertion of LNG-IUS, although a direct causal relationship to LNG-IUS cannot always be confirmed. Around 15–20% of LNG-IUS users experience at least one or more unwanted side effects [5,106,107]. The most frequent (around 10–15% of users) is unscheduled erratic menstrual bleeding, which usually occurs during the first 3–4 months following LNG-IUS insertion but tends to subside thereafter. Erratic irregular menstrual bleeding is cited by women as the most common reason for discontinuing LNG-IUS treatment.

During LNG-IUS use, 17.5% of women had a cyst at 6 months (diameter over 3 cm) and 21.5% at 12 months [55]. The vast majority of these were asymptomatic and functional, and exhibited a high rate (94%) of spontaneous resolution by 6 months [55]. Other less common side effects include mastalgia, migraine, acne, weight gain, oedema, labile mood, abdominal pain, pelvic pain, nausea and coil-related (infection, perforation, spontaneous expulsion) complications [35,101,102]. Nevertheless, the continuation

and patient satisfaction rates in women using LNG-IUS for contraception remains over 75% [98,108–111].

Studies conflict on whether the induction of amenorrhoea is considered a desired effect [98] or an unwanted side effect [5,35] that may lead to LNG-IUS discontinuation. This determination is based on the individual's clinical symptomatology pre-LNG-IUS insertion. Amenorrhoea occurs following LNG-IUS insertion in 20–60% of normally menstruating women using the device for contraception, between 50% and 75% in women with menorrhagia and 61–100% in postmenopausal women using the device to protect the uterus during estrogen replacement therapy [9,35,42,75,82,97,107,108,112].

4. Discussion

Our systematic review has shown strong evidence that LNG-IUS is effective in treating women with idiopathic menorrhagia and in providing uterine protection for women receiving estrogen replacement therapy or tamoxifen. There is preliminary evidence that shows LNG-IUS may be therapeutic in women with fibroids, endometriosis, adenomyosis, endometrial hyperplasia, early stage endometrial cancer and dysmenorrhoea and may reduce the risk of pelvic inflammatory disease. The grading of evidence is depicted in Table 1. The incidence of adverse effects, in particular initial period of erratic menstrual bleeding, is unaffected by the indication for the use of LNG-IUS. The incidence of amenorrhoea following LNG-IUS insertion appears to be influenced by age and independent of underlying gynaecological pathology: the incidence is greater in postmenopausal women than premenopausal women, and is usually achieved by 1-year duration of LNG-IUS use.

This review has been original in systematically collecting and presenting the data relating to LNG-IUS use in HRT, tamoxifen, endometrial hyperplasia, endometrial cancer, endometriosis and adenomyosis. The systematic search strategy employed was comprehensive and methodological analysis followed standardised criteria. This review has updated and expanded on studies listed in the Cochrane database [40,41,113] and a previous related systematic review [11]. Our findings complement the recently published Cochrane protocol on post-operative LNG-IUS in endometriotic surgery [113], and supplements the evidence reported in a Cochrane review of pre- and post-operative medical therapy for endometriotic surgery which had excluded LNG-IUS usage [114]. Our review has included recent developments, such as data from lower dose LNG-IUS devices currently under development (e.g. FibroPlant™-LNG) and health related quality of life assessments for women using LNG-IUS [14].

We observed a general paucity of RCTs, varying study methodologies and outcome measures, which made the interpretation of study data difficult and prevented us from performing a meta-analysis. We had intended to perform a

systematic review of LNG-IUS, and instead this review is a narrative assimilation of the available literature. Furthermore, our systematic search strategy may have missed relevant studies. However, by maintaining a sensitive keyword search, contacting the manufacturer Schering for unpublished studies and checking registered clinical trials databases, we believe this loss has been minimised. Apart from menorrhagia and HRT therapeutic indications, the published literature mainly consists of limited sample-sized (below 50 participants in LNG-IUS arm of study) non-controlled observational studies with less than 1-year follow up, which although showing consistent trends, are likely to be subject to information and selection biases. Consequently, no firm conclusions can be inferred from these studies (evidence grading C). However, these studies may provide a basis to estimate minimum numbers needed to be recruited to demonstrate clinically significant results in future therapeutic trials using LNG-IUS.

There is strong evidence demonstrating the efficacy, cost-effectiveness and safety of LNG-IUS in menorrhagia. This evidence has been translated to clinical practice through recent licensing (2001) of LNG-IUS for women with menorrhagia. A similar abundance of RCTs, cohort and observational evidence, demonstrating efficacy and endometrial safety, exists for the use of LNG-IUS in providing endometrial protection during estrogen replacement therapy. Research in to this modality of HRT has been abundant since its inception in the late 1980s [115,116]. However, unlike menorrhagia, the license for HRT use has not been forthcoming in many countries, and was only awarded this year (2005) in the UK.

The Women's Health Initiative and Million Women Study, showed HRT use increased the risk of stroke, pulmonary embolism and breast cancer, but decreased risk of hip fracture, with no effect on coronary heart disease incidence [117–120]. Incidence of breast cancer was significantly increased for users of hormone replacement therapy containing estrogen only (1.30 [1.21–1.40]), estrogen–progestogen (2.00 [1.88–2.12]) and Tibolone (1.45 [1.25–1.68]), but the magnitude of the associated risk was substantially greater for estrogen–progestogen than for other types of HRT. The reluctance to use LNG-IUS may be based on concerns that stable systemic levels of levonorgestrel (330–350 pg/ml) [1] may be sufficient through its progestogenic effect to promote tumourigenesis in the breast (particularly if given with exogenous estrogen) or blunt the anti-tumour effect of tamoxifen on the breast. Similarly, it is plausible to extrapolate the endometrial suppression data observed in the perimenopausal hormone replacement therapy, tamoxifen and endometrial hyperplasia studies and hypothesize that the risk of endometrial cancer may be reduced in long-term users of LNG-IUS. However, we found no data relating LNG-IUS use to an increased or decreased risk of breast or endometrial cancer risk. However, absence of publications showing association does not necessarily indicate a lack of association between LNG-IUS and cancer.

We believe this to be an important safety issue that remains to be addressed, either through long-term follow up and re-analysis of published studies or further prospective trials.

Despite promising findings, further trials are needed to establish efficacy, safety, cost-effectiveness and quality of life measures before recommending LNG-IUS in most of the non-contraceptive indications discussed. Studies need to identify which population groups benefit most from LNG-IUS use, and this is made difficult due to the varying spectrum of disease, co-existence of multiple gynaecological pathology, and whether LNG-IUS is being tested as a first line or second line treatment following failed medical or surgical intervention. For example, subgroup analysis of trial data has shown that the magnitude of baseline menstrual blood loss was negatively predictive of successful treatment with LNG-IUS [121]. The authors and manufacturers of the newer lower dose and smaller sized LNG-IUS devices assert they are easier to insert, have less adverse side effects and greater patient acceptability [3,67,68,83] than conventional 20 mcg/24 h LNG-IUS. However, there is little supporting evidence for this assertion, and these devices need to be rigorously evaluated in robust head-to-head comparisons with conventional LNG-IUS to validate this viewpoint.

There is a paucity of data on patient preference and decision analysis strategies in the use of LNG-IUS [8]. This research should accompany future trials, particularly given the number of competing similar efficacy therapeutic medical and surgical interventions. A recent questionnaire study highlighted how patient's choice of treatment is influenced by several factors. These may include the likelihood of whether the treatment will be completely successful, prolonged hospital stay and convalescence, and preservation of future fertility. The majority of women scheduled for an endometrial ablation or LNG-IUS for menorrhagia were inclined to take a risk of 50% likelihood of treatment failure to avoid a hysterectomy [122].

LNG-IUS can no longer just be considered suitable for women with menorrhagia who wish reversible contraception. The fact that so many conditions in gynaecology are likely to be amenable to LNG-IUS underlies the importance of progestogens in the normal and pathological female genital tract. This review's findings complement the current resurgence of basic science research interest in this area and clinical trials evaluating potential therapeutic use of selective progesterone receptor modulators in the conditions discussed in this review [123]. This review has provided a foundation to undertake robust research trials in this area that could potentially show greater therapeutic benefit and lesser patient harm when using LNG-IUS compared to currently available medical and surgical therapies.

Note added in proof

Since completion and journal acceptance of this review the authors wish to highlight a recent study, published after

our literature search that has helped to clarify a question posed in the discussion. A population wide survey of Finnish women has shown LNG-IUS is not associated with an increased risk of breast cancer (Backman et al. [124]).

Conflict of Interest

JKG is in receipt of a HTA grant to examine the therapeutic use of LNG-IUS in the treatment of menorrhagia in primary care (ECLIPSE trial). RV and DS declare no conflicts of interest.

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