Levonorgestrel-releasing intrauterine system (LNG-IUS)

This presentation includes data on the LNG-IUS 52 mg (LNG 20 IUS), LNG-IUS 13.5 mg (LNG 12 IUS) and LNG-IUS 19.5 mg (LNG 16 IUS).

This advanced slide kit is complementing the WHO training tool which can be found at www.fptraining.org

Update August 2020 K.S., A.K., G.M., F.R.

This session was updated by Katarina Sedlecky with support of Ali Kubba, Gabriele Merki and Frans Roumen.
Contents

To enable clinicians and trainers to understand and explain:

- What is the hormone-releasing intrauterine system (IUS) and why was it developed
- General characteristics of the levonorgestrel (LNG) IUS
- Mechanism of action of the LNG-IUS
- Contraceptive efficacy of the LNG-IUS
- Adverse and serious adverse events, treatment of bleeding
- Reasons for discontinuation of the LNG-IUS
- Medical indications for LNG 20 IUS

2 - A literature review identified four studies regarding extended use of the LNG-IUS, which is approved for 5 years of use. Based on cumulative, international data, the LNG-IUS appears to be highly effective for pregnancy prevention up to 7 years among parous women whose mean age is greater than 25 at the time of insertion; no pregnancies were reported between years 5 and 7 in all four studies.

3 - An open-label 7-year randomized controlled trial in 20 centres, 11 of which in China. Data on 1884 women with interval insertion of the LNG-IUD and 1871 of the TCu380A were analysed. The cumulative 7-year pregnancy rate of the LNG-IUD was 0.5 (standard error 0.2) per 100, and 2.5 (0.4) per 100 of the TCu380A. Thirty-three pregnancies occurred among TCu380A users of which three were ectopic. Seven pregnancies occurred among LNG-IUD users, all intrauterine. No pregnancy occurred in the 1342 woman-years of observation of the TCu380A and 681 of the LNG-IUD from 8 to 11 years, based on 682 TCu380A and 398 LNG-IUD users starting the eighth year of use, respectively. In LNG-IUD users all pregnancies occurred within the first five days of use.

4 - Systematic review of the literature to determine if extended use of intrauterine devices, including the copper or levonorgestrel intrauterine device, beyond approved durations is effective and safe for preventing pregnancy. Of 4068 studies identified, 4 good-to-poor-quality studies of the 52 mg levonorgestrel intrauterine device (approved for 5 years), with a total of 2098 women starting extended use, and 2 good-to-fair-quality studies of the T380A copper intrauterine device (approved for 10 years), with 245 women starting extended use, met inclusion criteria. For the levonorgestrel intrauterine device, the pooled pregnancy rate was 0.02 per 100 person-years (95% confidence interval, 0.00-0.45) in year 6, 0.03 per 100 person-years (95% confidence interval, 0.00-0.71) in year 7, and 0.02 per 100 person-years (95% confidence interval, 0.00-0.29) in years 6 and 7 combined. For the copper intrauterine device, the pooled pregnancy rate for years 11 and 12 was 0.0 per 100 person-years (95% confidence interval, 0.0-0.8), and annual rates of adverse events and discontinuation owing to side effects during extended use ranged from 0 to 4.6 per 100 participants. Data were limited in quantity and quality, and may not be generalizable to all intrauterine device users.
Topic: LNG-IUS

Differences between LNG-IUs

| LNG 20 IUS | Additional health benefit: profound reduction in menstrual blood loss. Contraceptive efficacy 5 years. (size of the vertical stem 32 mm and inserter 4.44 mm/4.75 mm) |
| LNG 12 IUS | Smaller frame and inserter diameter. Contraceptive efficacy 3 years. (size of the vertical stem 30 mm and inserter 3.75 mm) |
| LNG 16 IUS | Smaller frame and inserter diameter. Contraceptive efficacy 5 years. (size of the vertical stem 30 mm and inserter 3.75 mm) |

Ref 1-6


In most (>98%) women, IUS insertion was successful on the first attempt. More than 85% of IUS insertions were rated as easy by health care professionals. Most women did not experience significant pain during IUS insertion. Smaller and lower-dosed LNG-IUS (LNG 12 IUS, LNG 16 IUS) have been developed to facilitate insertion in nulliparous women. However, the pain and ease of IUS insertion depends on many factors, among which the experience of the clinician performing the procedure is very significant. These lowered dosed LNG IUS do not typically inhibit ovulation and have less impact on duration and intensity of the monthly bleeding. They are not licensed for use in heavy menstrual bleeding. Additionally, there are data indicating that LNG 20 IUS might be effective for more than 5 years.

Ref 2 - The review aimed at comparing the pharmacological and mechanical properties of Jadess/Skyla (LNG 12 IUS) and Kyleena (LNG 16 IUS), together with their clinical features with that of the Mirena (LNG 20 IUS) and its generic versions, so that clinicians can make a rational choice about which intrauterine contraceptive (IUC) to use and in which circumstance. There were 8 complete studies and 11 conference proceedings abstracts of Jadess/Skyla and Kyleena in comparison to Mirena or compared within different clinical groups (nulliparous and nulligravidae (NR) and parous), and two studies comparing Jadess with other types of contraceptives (implant® and Yaz® (30 µg ethinyl estradiol/3 mg desogestrel) oral contraceptives). All the reported studies were sponsored by the manufacturer of Jadess/Skyla and Kyleena.

Ref 3 - There are differences in physical characteristics of LNG-IUSs, specifically in the size and presence of the silver ring. Thus, newer types of LNG-IUS should facilitate insertion and improve tolerance to IUS in adolescents and nulliparous women.

Ref 4 - Systematic review of the literature to determine if extended use of intrauterine devices, including the copper or levonorgestrel intrauterine device, beyond approved durations is effective and safe for preventing pregnancy. Results: Based on 4 good to poor-quality studies of the 52 mg levonorgestrel intrauterine device (approved for 5 years), with a total of 2088 women starting extended use, the pooled analyses of 2088 women starting extended use, the pooled analyses of the available evidence suggest that rates of pregnancy, adverse events, and discontinuation owing to side effects during the first 2 years of extended use of the 52 mg levonorgestrel intrauterine device are low and comparable to rates during approved duration of use. Data were limited in quantity and quality, and may not be generalizable to all intrauterine device users.


Ref. 1 – To assess the pharmacokinetics and pharmacodynamics of levonorgestrel intrauterine system (LNG-IUS) a randomized, open-label, multicenter phase II and III studies were conducted that included 742 nulliparous and parous women randomized to 3 years' treatment with LNG 12 IUS, LNG 16 IUS, or LNG 20 IUS. The in vivo LNG release rate of LNG 12 IUS was approximately 14 mg/24 h after 24 days, declining progressively to 5 mg/24 h after 3 years. The average LNG serum concentration over 3 years of use was 74.3 ng/L, 114 ng/L, and 218 ng/L for LNG 12 IUS, LNG 16 IUS, and LNG 20 IUS, respectively.

Ref. 2 - To compare the pharmacokinetics (PK) of the progestin levonorgestrel for various routes of administration, an integrated population PK analysis was performed. This analysis integrated data from 10 clinical pharmacology studies and resulted in a single, comprehensive population PK model (and its applications) describing the PK of levonorgestrel and its variability for 6 levonorgestrel-containing contraceptives: 3 intrauterine systems (LNG 20 IUS, LNG 16 IUS and LNG 12 IUS); 2 oral contraceptives (the progestinonly pill and the combined oral contraceptive); and a subdermal implant.

Results: The levonorgestrel containing contraceptives administered orally or as an implant act mainly via their systemic (unbound) levonorgestrel exposure, whereas levonorgestrel administered via an IUS is released directly into the uterine cavity, resulting in lower systemic levonorgestrel concentrations. The integrated population PK analysis revealed that the combined oral contraceptive led to the highest levonorgestrel exposure, followed by the progestin-only pill and the implant, which led to similar levonorgestrel exposure that is two to three times higher compared to and the IUSs, which led to the lowest levonorgestrel exposure (in decreasing order: LNG 20 IUS, LNG 16 IUS, and LNG 12 IUS). In LNGs users LNG serum levels decrease over time, from initial 200 ng/L, 150 ng/L and 130 ng/L in LNG 20 IUS, LNG 16 IUS and LNG 12 IUS users to 133 ng/L, 85 ng/L and 58 ng/L at the end of the duration of IUSs use. The difference in serum LNG concentrations between IUSs was even more pronounced at the end of the indicated duration of use (3 years for LNG 12 IUS and 5 years for both LNG 20 IUS and LNG 16 IUS).
**Mechanism of action of the LNG-IUSs**

**ENDOMETRIUM:**
- alteration of endometrial receptivity
- suppression of endometrial proliferation
- local inflammatory reaction (foreign body reaction)

**CERVICAL MUCUS:**
- inhibition of sperm migration
- thickening of cervical mucus

**OVARY**
- Some dose-dependent effect on follicular development and inhibition of ovulation

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Ref. 1 - To assess the pharmacokinetics and pharmacodynamics of levonorgestrel intrauterine system (LNG-IUS) a randomized, open-label, multicenter phase II and III studies were conducted that included 742 nulliparous and parous women randomized to 3 years’ treatment with LNG 12 IUS, LNG 16 IUS, or LNG 20 IUS. All treatments showed very similar progestogenic effects on cervical mucus, with low and similar cervical scores throughout treatment. Ovulation was observed in the majority of women in all groups where assessment was possible, although there was a lower incidence of anovulation with LNG 12 IUS and LNG 16 IUS compared with LNG 20 IUS. The progestogenic effect on the endometrium was marked in all three LNG-IUS groups.

Ref. 2 - Ovarian function was studied for two complete menstrual cycles in 9 regularly menstruating women and for 8 weeks in three amenorrhoeic women who had used levonorgestrel-releasing IUDs (LNG 20 IUS) for more than four years. Nine patients using copper IUDs (Nova-T) were studied for two complete menstrual cycles as controls. According to progesterone levels, 15/17 cycles in women using LNG 20 IUS were ovulatory, whereas only 8/17 cycles showed normal follicular growth and rupture as judged by ultrasound. In ovulatory cycles, the peak progesterone levels were lower than in the controls. The preovulatory estradiol and LH peak levels were also lower than in control subjects. SHBG levels were lower in LNG-IUS users than in copper IUD users. It is concluded that, although the dose of levonorgestrel released from the IUS is very low, it probably exerts an effect on the gonadotrophin secretion, which disturbs follicular development in many of the women studied, which in addition to the local effect on the endometrium, contributes to its high contraceptive efficacy.

Ref. 3 - In the study 14 women after 6 years’ use of levonorgestrel-releasing IUD were investigated for the changes of LH, progesterone (P), estradiol (E2), prolactin (PRL) and serum binding globulin (SHBG) in relation to the levonorgestrel levels throughout a segment of 26-40 days with the aim of comparing the hormonal profiles with those during the first year of use of LNG 20 IUS. Ultrasound scanning was used to follow the development of follicles along with the RIA measurement of hormones. It is concluded that over two-thirds of the cases have ovulatory cycles after long-term use of LNG 20 IUS; the contraceptive effect is mainly due to its local action on the endometrium, with much less effect on the ovarian function.
Contraceptive efficacy and ectopic pregnancy rates in LNG-IUS users.

### LNG IUS

<table>
<thead>
<tr>
<th>LNG IUS</th>
<th>Cumulative 3/5-years Pearl index (all pregnancies/100 woman-years)</th>
<th>Ectopic pregnancy rate for the first year of use (ectopic pregnancies/100 woman-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG 20 IUS</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>LNG 16 IUS</td>
<td>0.29</td>
<td>0.18</td>
</tr>
<tr>
<td>LNG 12 IUS</td>
<td>0.2 – 0.3</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The risk for ectopic pregnancy is lower in users of all three types of LNG-IUS than in women without contraception.

Ref. 1-9

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Adverse events of LNG-IUSs

<table>
<thead>
<tr>
<th>Three-years adverse events (%)</th>
<th>LNG 20 IUS</th>
<th>LNG 16 IUS</th>
<th>LNG 12 IUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestin related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Altered mood</td>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Acne</td>
<td>28</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Breast pain/discomfort</td>
<td>7/22</td>
<td>11/18</td>
<td>6/19</td>
</tr>
<tr>
<td>Increased weight</td>
<td>8</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Other adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>9.8</td>
<td>8.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>22</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>


Ref. 1 – In a randomized, open-label, three-arm, phase II study a total of 742 parous or nulliparous women aged 21–40 years from 37 centers in five European countries were randomized. 738 (99.5%) of whom had an LNG-IUS successfully placed (LNG-IUS12, n = 239/240; LNG-IUS16, n = 245/246; LNG-IUS20, n = 254/256). Main Outcome Measure(s); Pearl index, bleeding profile, ease/pain of placement/removal, adverse events. The bleeding profile were similar in all groups, although total bleeding and spotting days decreased with increasing LNG dose. During 3 years, 10 subjects in the LNG-IUS12 (2 women), LNG-IUS16 (3 women), and LNG-IUS20 (5 women) groups reported serious adverse events, possibly related to study treatment. Placement of LNG-IUS 12 and LNG-IUS 16 was considered easy in 94% versus 86.2% in the LNG-IUS20 group and 72.3% in the LNG-IUS12/LNG-IUS16 group reported either “no pain” or only “mild pain” during placement versus 57.9% in the LNG-IUS20 group.

Ref 2 – In a Phase III study in 36 European centers, 304 healthy nulliparous or parous postmenarcheal adolescents (12–17 years) received LNG-IUS 8 for 12 months. The primary outcome was the incidence of treatment-emergent adverse events (TEAEs). Secondary outcomes included: serious TEAEs, adverse events of special interest, overall user satisfaction, discontinuation rate at 12 months, and Pearl Index. RESULTS: LNG-IUS 8 placement was successful in 303/304 participants (99.7%). Overall, 83.6% of participants reported TEAEs, and serious TEAEs and serious study drug-related TEAEs were reported by 7.6% and 1.0% of participants, respectively. No cases of pelvic inflammatory disease, ectopic pregnancy, or uterine perforation were reported. No pregnancies were reported during the 12-month study. At Month 12 study end, the overall user satisfaction rate was 83.9%. Overall, 54 participants (16.8%) prematurely discontinued the study before 12 months; 13.8% of participants discontinued owing to TEAEs.

Ref. 3 - To evaluate the efficacy and safety of a new, low-dose levonorgestrel intrauterine contraceptive system (LNG-IUS 12) for up to 5 years of use in this Phase III study, 2885 nulliparous and parous women aged 18–35 years were randomized to LNG-IUS 8 or LNG-IUS 12 for 3 years. After 3 years, women using LNG-IUS 12 could continue for up to 2 additional years (5 years total). The primary outcome was occurrence of pregnancy (Pearl Index). Secondary outcomes included safety, bleeding, dysmenorrhea, discontinuations, and user satisfaction. RESULTS: Of 2885 women who were enrolled, 1453 were randomized to LNG-IUS 12. Placement was attempted in 1452/1453 (full analysis set). Mean age at baseline was 27.1 years; 39.5% were nulliparous. The cumulative 5-year Pearl Index (PI) was 0.29; the 5-year cumulative failure rate was 1.4%. The 5-year PI for ectopic pregnancy was 0.18. Over 5 years, 55.3% of women reported study drug-related treatment-emergent adverse events (TEAEs). Crude incidences of pelvic inflammatory disease, uterine perforation, and complete/partial LNG-IUS 12 expulsion were 0.6%, 0.2%, and 3.7%, respectively. The incidence of amenorrhea during the last 90-day reference interval (end of Year 5) was 22.6%. Overall, 550 (37.9%) women completed 5 years of treatment with LNG IUS 16; 77.8% of women who entered the extension phase completed 5 years of use. Over 5 years, 22.6% discontinued due to TEAEs, including 13 women who discontinued due to pregnancy; 76 discontinued due to bleeding problems including amenorrhea; and 163 discontinued due to desire for pregnancy, 71.2% of whom conceived within 12 months.
Early removal of the LNG-IUSs varies between studies

**Overall 1 year discontinuation rate: 7.3% - 27%**

<table>
<thead>
<tr>
<th>Reason for requesting removal</th>
<th>Termination rate per 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or cramping</td>
<td>2 - 13 %</td>
</tr>
<tr>
<td>Bleeding problems</td>
<td>2 - 26 %</td>
</tr>
<tr>
<td>Hormonal side effects: headaches, nausea, hair loss, breast tenderness, depression, decreased libido, acne, increased weight</td>
<td>1 - 5 %</td>
</tr>
</tbody>
</table>

Adolescents and nulliparous women tend to have higher removal rates for pain. This might be less with a smaller device.

Hormonal side effects are rarely the reason for requesting removal of the LNG-IUS. There are big differences in discontinuation rates that are largely related to cultural factors. Women with different socio-cultural backgrounds accept and tolerate amenorrhea and prolonged or frequent bleeding, as well as pain or cramping in different ways.


Ref. 1 – Randomized, open-label, three-arm, phase II study. Setting: Thirty-seven centers in five European countries. Patient(s): Parous or nulliparous women aged 21–40 years. Intervention(s): Treatment with LNG-IUSs with initial in vitro release rates of 12 or 16 mg/d (LNG-IUS12/16) or 20 mg/d. Main Outcome Measure(s): Pearl index, bleeding profile, ease/pain of placement/removal, adverse events. Result(s): A total of 738 subjects had an LNG-IUS placed (LNG-IUS12, n = 239; LNG-IUS16, n = 245; LNG-IUS20, n = 254). In the LNG-IUS12, LNG-IUS16, and LNG-IUS20 groups, the proportion of subjects with amenorrhea increased from 2.7%, 6.1%, and 5.9%, respectively, in the second 90-day reference period to 12.7%, 18.9%, and 23.6% of subjects, respectively, in the final 90-day reference period (P=.012 for LNG-IUS12 vs. LNG-IUS20, P=.30 for LNG-IUS16 vs. LNG-IUS20 for the final reference period).

Ref. 2 - The purpose of this study was to investigate the validity of existing prevalence estimates by the systematic calculation of amenorrhea measures for a general population of levonorgestrel intrauterine system users and to provide 90-day interval point estimates for the first year of use. Of 2938 potentially relevant studies, we included 9 in our meta-analysis. Results demonstrated that few levonorgestrel intrauterine system users (0.2%; 95% confidence interval, 0.0-0.4) experienced amenorrhea during the first 90 days after insertion; however, prevalence increased to 8.1% (95% confidence interval, 6.6-9.7) on days 91e180. Finally, 18.2% (95% confidence interval, 14.9-21.5) of users experienced amenorrhea for at least 1 90-day interval during the first year. Although interstudy heterogeneity limited reliability of days 181-271 and 272e365 measures, prevalence increased from 13.6% (95% confidence interval, 9.3-18.0) to 20.3% (95% confidence interval, 13.5-27.0), respectively. CONCLUSION: Approximately 20% of levonorgestrel intrauterine system users experience amenorrhea during at least 1 90-day interval by the first year after insertion.

Frequent, prolonged and irregular bleeding episodes tend to decrease, while infrequent bleeding rates increase over time in users of all three types of LNG IUS.

Ref. 1 - Available data on bleeding patterns were extracted from published sources. Lower dose products had published data at 1 and 3 years; the 52 mg IUS had available data for 1, 2 and 3 years for amenorrhea and 1 and 2 years for other bleeding patterns. 2-year data for the lower dose products were interpolated based on 1- and 3-year data and compared bleeding pattern rates using Fisher exact testing. Results: The studies evaluated bleeding patterns in 1700, 1566 and 1531 women using levonorgestrel 52 mg, 19.5 mg and 13.5 mg products, respectively. **Infrequent bleeding rates were higher for 52 mg users** by the end of year 1 (31%) compared to 19.5 mg (26%, \(p=.01\)) and 13.5 mg (20%, \(p<.0001\)). **Frequent and prolonged bleeding patterns were similar over the first 2 years for all products**, although the rates were statistically higher for levonorgestrel 13.5 mg IUS users compared to 19.5 mg and 52 mg IUS users (\(p<.03\) for all time points after 90-days post-insertion). **Irregular bleeding rates were higher with the lower dose products** by 90 days after insertion with continued lower rates at the end of year 1 for 52 mg users (6%) compared 19.5 mg (17%, \(p<.0001\)) and 13.5 mg (23%, \(p<.0001\)). Conclusions: Levonorgestrel 52 mg IUS users have more infrequent bleeding and less irregular bleeding compared to women using lower dose levonorgestrel IUS products.

Legend:
- Infrequent bleeding One or two bleeding/spotting episodes during a 90-day reference period
- Frequent bleeding More than five bleeding/spotting episodes during a 90-day reference period
- Prolonged bleeding Bleeding/spotting episodes lasting more than 14 days during a 90-day reference period
- Irregular bleeding Three to five bleeding/spotting episodes and less than three bleeding/spotting-free intervals of 14 days or more during a 90-day reference period
Management of irregular bleeding with the LNG-IUS

In the first 3-6 months of LNG-IUS use: reassurance, if no other symptoms - exclude STIs or suspicion of a pregnancy

After 6 months - exclude gynaecological pathology, STIs/PID, pregnancy, etc.

Treatment options:
- Not effective: tranexamic acid, mefenamic acid, ulipristal acetate
- Some benefits: nonsteroidal anti-inflammatory drugs (NSAIDs)
- Empirical treatment: transdermal estrogen 7 days or short-course (21 days) 30 μg EE COC (only in women without risk factors); doxycycline 2x100mg for 5 days; tamoxifen 2x10mg for 7-10 days (off label).

Ref 1-5


Ref. 1 – Randomised trial to assess the efficacy of tranexamic acid or mefenamic acid in the management of the initial “nuisance” bleeding or spotting in the period immediately after placement of the levonorgestrel-releasing intrauterine system. Women were randomised after levonorgestrel-releasing intrauterine system placement to oral tranexamic acid (500 mg), mefenamic acid (500 mg), or placebo three times daily during bleeding or spotting episodes over a 30-day treatment period. Treatment was initiated from onset of a bleeding or spotting episode and continued until the first day after menstruation by starting and stopping daily in women on the treatment. Women had no prior use of oral contraceptive pill. Results: 436 women randomised to one of three arms: placebo (P), tranexamic acid (TA) or mefenamic acid (MA). The median number of bleeding or spotting days experienced during treatment was 25, 26, and 31 days in the three groups, respectively. The median number of bleeding or spotting days was reduced by 4 days (95% confidence interval [CI] 1.4 to 6.2; P < 0.001) with tranexamic acid and by 3 days (95% CI 1.2 to 5.0; P < 0.001) with mefenamic acid compared with placebo. The relative risk of bleeding or spotting compared with placebo with tranexamic acid and mefenamic acid was 0.82 (95% CI 0.80-0.84) and 0.89 (95% CI 0.87-0.91), respectively. Conclusions: Tranexamic acid and mefenamic acid during the first 30 days after levonorgestrel-releasing intrauterine system placement do not alleviate “nuisance” bleeding or spotting.

Ref. 2 – A double-blind randomized controlled trial of women aged 19-49 years, newly starting use of LNG-IUS to determine whether intermittent administration of progesterone receptor modulator CDB-2914 would suppress unscheduled bleeding during the first 4 months after insertion of the LNG-IUS. Methods: CDB-2914 150 mg, in divided doses, or placebo tablets, were administered over three consecutive days starting on Days 21, 49 and 77 after LNG-IUS insertion. Daily bleeding diaries were completed for 6 months, and summarized across blocks as percentage days bleeding/spotting (BS%). Results: Of 69 women randomised to receive CDB-2914, and 61 placebo, 65 and 55, respectively, completed the trial. BS% decreased with time in both arms, but showed a much steeper treatment-time gradient in the placebo arm (β = 0.0001), so that a benefit of CDB-2914 in the 28 days after first treatment (1.1% points, 95% CI 1.0% to 1.2%), converted to a disadvantage by 64 days after the third treatment (+0.02 points, 95% CI 1.1% to 1.3%). Conclusions: The effect of CDB-2914 on BS% was initially beneficial but then by third treatment was disadvantageous. Nevertheless, only 3% (4/136) of all women discontinued LNG-IUS.

Ref. 3 – A randomized controlled trial of naproxen, estradiol, or placebo that was administered over the first 12 weeks of levonorgestrel-releasing intrauterine system use. There were 125 women who were assigned randomly to naproxen (N = 42 women), estradiol (N = 44 women), or placebo (N = 43 women). The naproxen group was more likely to be in the lowest quartile of bleeding and spotting days compared with placebo (42.9% vs 16.2%; P < 0.05). In the multivariate analysis, the naproxen group had a 10% reduction in bleeding and spotting days (adjusted relative risk 0.90; 95% confidence interval, 0.84–0.97) with placebo. More frequent bleeding and spotting was observed in the estradiol group (adjusted relative risk, 1.25; 95% confidence interval, 1.17–1.34).

Ref. 4 – A double-blind trial, LNG implant users with frequent bleeding or spotting who were randomized to tranexamic acid 10 mg or placebo twice daily for 7 days, to be started after 4 consecutive days of bleeding/spotting. Treatment was repeated as needed up to three times in 180 days. Subjects completed a daily text message bleeding diary. Altogether 50 women were enrolled, 51 completed at least 30 days of follow up, and 34 completed 180 days. Compared to women randomized to placebo, women randomized to tranexamic acid reported 5 fewer days of bleeding/spotting over 30 days (95% confidence interval [CI] 0.5 to 10.5; P = 0.03), and 1.9 more continuous bleeding-free days (95% CI 0.8-2.7 days, P = 0.03) after first use of study drug. Conclusions could not be drawn after 30 days due to higher-than-expected dropout. No ovulation was detected.

Ref. 5 – Cochrane review addressing whether non-steroidal anti-inflammatory drugs (NSAIDs) helped reduce heavy menstrual bleeding (HMB) in women before they reach the menopause. Background: NSAIDs reduce prostaglandin levels, which are elevated in women with excessive menstrual bleeding. It was suggested that they might help with heavy bleeding and may have a beneficial effect on painful menstrual periods. Study characteristics: Authors searched medical databases and identified 10 randomized controlled trials (RCTs), clinical studies where people are randomly put into one of two or more treatment groups) with 707 women that could be included in the review, but data from only nine trials were suitable for analysis. Key results: Women sought help for HMB when it affected their quality of life. They preferred medical treatment to other medicines, such as danazol, tranexamic acid and levonorgestrel-releasing intrauterine system (LNG-IUS), as more effective. These results were based on a small number of low- to moderate-quality trials.
### Expulsion of the LNG-IUS

<table>
<thead>
<tr>
<th>Exclusion rate (complete and partial) over 3/5 years</th>
<th>LNG 20 IUS</th>
<th>LNG 16 IUS</th>
<th>LNG 12 IUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 – 6.3%</td>
<td>2 – 3.6%</td>
<td>0.4 - 4.6%</td>
<td></td>
</tr>
</tbody>
</table>

**About half of all LNG-IUS exclusions occur during first six months.**

The number of complete exclusions is approximately equal to the number of partial exclusions of the LNG-IUS.

**Ref. 1 - 8**


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**Ref.**

Breast cancer risk in premenopausal LNG 20 IUS users

- Two newer high quality registry-based studies (including women aged 18-49 years observing > 500000 wy of use) found a minimal but significant risk increase for current users: RR 1.2 *(Ref 1,2)*.

- Numbers *(Ref 1)*
  - Non-hormonal contraception 55 cases/100000 wy
  - LNG-IUS 70 cases/100000 wy

- The LNG-IUS should not be used in women with breast cancer and as contraceptive after breast cancer!

An increased risk for older peri- and postmenopausal women was not found *(Ref 3,5)*


3) **Jareid et al.** Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study Large cohort study: Norwegian Women and Cancer Study, 104,318 women, 9,144 ever users and 95,174 never users of LNG-IUS. Adjusted on risk factors

4) **Siegelmann-Danieli N.** Breast Cancer Res Treat 2018;167:257–262.

5) **Lyytinen et al,** A case-control study on hormone therapy as a risk factor for breast cancer in Finland: Intrauterine system carries a risk as well.Int J Cancer. 2010 Jan 15;126(2):483-9

Finish women 50 – 62 years [1995-2007]; 329 cases users vs 708 controls ; Note the ages of the population. In menopausal transition 287 cases Mirena®+E2 vs 473 controls

*Ref 1:* The data were collected from a Danish Cancer registry 1995-2012. Included women were 14-49 years old. It reports 11517 incident breast cancers in 1.8 million women. Observation of >500000 wy LNG-IUS use, 70 BC cases in LNG 20 –IUS users compared with 55 cases in the control group. Adjusted for age, family history parity, education, PCOS.

*Ref 2:* Registry based finish cohort study in women aged 30-49 years; 93000 LNG-IUS users and 1032000 wy of observation. No adjustments but duration of use increased the BC risk further in this study. Significance was only found for more than 5 years duration of use.

*Ref 3:* Large cohort study: Norwegian Women and Cancer Study, 104,318 women, 9,144 ever users and 95,174 never users of LNG-IUS. Interview-based. Mean age of women: 52 years (range 41-76) Adjusted on risk factors

*Ref 4:* Israeli case control study in population. 13,354 LNG-IUS users and 27,324 controls (mean age: 44.1 ± 2.6 vs. 44.9 ± 2.8 years. Non significant trend to a small increase only in women 40-45 years

*Ref 5:* Postmenopausal Finish women 50 – 62 years [1995-2007]; 329 cases users vs 708 controls ; Note the ages of the population. In menopausal transition 287 cases LNG-20 IUS+E2 vs 473 controls
Advantages of the LNG-IUS

- No negative impact on bone mineral density
- No increase in venous thromboembolism (VTE)
- No increase in arterial risks
- No significant impact on metabolic cardiovascular and inflammatory parameters

Ref 1-7

   (In the case-control study to evaluate the association between postmenopausal hormone therapy (HT) and the risk for breast cancer in recently postmenopausal Finnish women was found that LNG-IUS used alone was associated with an elevated risk for breast cancer (1.45; 1.97–1.77), or as a complement to estradiol (2.15; 1.72–2.68) was also associated with an increased risk.)


Therapeutic uses for LNG 20 IUS

Effect of LNG on endometrium

Local daily release of LNG 20 µg/day

High LNG concentrations in endometrium ≈ 200-800 times higher than after daily oral dose

Low LNG plasma levels < 200 pg/mL

Inhibition of endometrial proliferation:
- reduced menstrual blood loss
- positive impact on dysmenorrhea
- mild hormonal and metabolic side-effects

LOCAL hormonal action
Periods. Excessive menstrual bleeding. It was suggested that they might help with heavy bleeding and may have a beneficial e-ect.

The period, calculated cumulative quality of life. Levels of prostaglandin (a inflammatory drug) are elevated in women with HMB and are reduced by NSAIDs. The review of trials found that NSAIDs were modestly effective in reducing HMB, but other medicines, such as danazol, tranexamic acid and levonorgestrel-releasing intrauterine system (LNG IUS), are more effective. These results were based on a small number of low- to moderate-quality trials.


Ref. 16 - In order to provide comparative estimates of clinical outcomes after placement of levonorgestrel-releasing intrauterine system (LNG-IUS), ablation, or hysterectomy for AUB, full articles published in 2006–2016 available in English comparing at least two treatment modalities of interest among women of reproductive age with AUB were included. A decision tree was generated to compare clinical outcomes in a hypothetical cohort of 100,000 premenopausal women with nonmalignant AUB. Authors evaluated complications, mortality, and treatment outcomes over a 5-year period, calculated cumulative quality-adjusted life years (QALYs), and conducted probabilistic sensitivity analysis. Levonorgestrel-releasing intrauterine system had the highest number of QALYs (406 920), followed by hysterectomy (403 466), non-resectoscopic ablation (399 244), and resectoscopic ablation (395 827). Ablation had more treatment failures and complications than LNG-IUS and hysterectomy. Findings were robust in probabilistic sensitivity analysis.

Ref. 17 - Ref. 3 - Cochrane review addressing whether non-steroidal anti-inflammatory drugs (NSAIDs) helped reduce heavy menstrual bleeding (HMB) in women before they reach the menopause. Background: NSAIDs reduce prostaglandin levels, which are elevated in women with excessive menstrual bleeding. It was suggested that they might help with heavy bleeding and may have a beneficial effect on painful menstrual periods. Study characteristics: Authors search medical databases and identified 19 randomised controlled trials (RCTs); clinical studies where people are randomly put into one of two or more treatment groups) with 759 women that could be included in the review, but due to only nine trials were suitable for analyses. Key results: Women sought help for HMB when it affected their quality of life. Levels of prostaglandin (a naturally occurring hormone) are higher in women with HMB and are reduced by NSAIDs. The review of trials found that NSAIDs were modestly effective in reducing HMB, but other medicines, such as danazol, tranexamic acid and levonorgestrel-releasing intrauterine system (LNG IUS), are more effective. These results were based on a small number of low- to moderate-quality trials.
The influence of LNG 20 IUS use on fibroid-associated heavy menstrual bleeding*

**Decrease in**

- bleeding intensity
- number of bleeding days
- myoma-related surgery

**• LNG-IUS is effective in selected women with fibroid-associated HMB (does not include submucous myoma)**

**• The size of the fibroids does not decrease markedly during treatment**

*Not a licensed indication for LNG 20 IUS use*

Ref 1-6


Ref. 6 - The objective of this systematic review was to evaluate evidence concerning the safety and effectiveness of IUD use among women with uterine fibroids. Results: From 202 articles found in the database search, 11 studies were identified that met our inclusion criteria, all of which examined outcomes among users of the levonorgestrel-releasing IUD (LNG-IUD). Evidence from 10 of 11 noncomparative studies (Level II-3, fair) suggests that LNG-IUD use among women with fibroids does not increase menstrual bleeding, and results from all 11 showed that menstrual blood loss decreased among women who continued to use the LNG-IUD through the end of the study period. Overall, serum levels of hemoglobin, hematocrit and ferritin increased among LNG-IUD users in studies that assessed these outcomes. Several studies reported some occurrences of irregular bleeding. Findings from two cohort studies (Level II-2, fair to poor) showed rates of LNG-IUD expulsion to be higher among women with uterine fibroids (11% in each) than among women without uterine fibroids (0% and 3%); however, in one study the difference was not statistically significant, and in the other significance testing was not conducted.


Ref. 1 - Copper-IUDs have been reported to exacerbate preexisting dysmenorrhea and cause pain. Dysmenorrhea is one of the reasons often quoted as a reason for cessation of intrauterine contraception or a reason for not starting intrauterine contraception. However, it is important to note that most trials do not specifically separate the reporting of dysmenorrhea from pain occurring between menstrual periods. In the study of Lindh and Milsom the prevalence and severity of dysmenorrhea were compared in a longitudinal analysis of variance performed in the same women using either intrauterine contraception (copper IUD or LNG-IUS) or COCs with other methods of contraception or no contraception. Random samples of 19-year-old women born in 1962 (n=656), 1972 (n=780) and 1982 (n=666) were assessed at 5 year intervals between 1981 and 2001. The current severity of dysmenorrhea was assessed on each occasion using a VMS and a VAS. The VMS is a scoring system which grades pain as none, mild, moderate or severe using grades 0, 1, 2 and 3, respectively. This scoring system also takes into account the effect on daily activity, systemic symptoms and whether analgesics are required. VAS is a technique where a 100 mm line on a paper represents the continuum of the woman's opinion of the degree of pain. Use of the LNG-IUS (p<0.01) and COC (p<0.0001) were associated with a reduced severity of dysmenorrhea compared with non-hormonal methods/no contraception. Copper-IUD has no significant impact on the severity of dysmenorrhea.

Ref. 2 - A total of 738 parous or nulliparous women aged 21–40 years had an LNG-IUS placed (LNG-IUS12, n=239; LNG-IUS16, n=245; LNG-IUS 20, n=254) were included to a 3 years’ treatment in a randomized, open-label, three-arm, phase II study in thirty-seven centers in five European countries. At baseline, absence of dysmenorrhea was reported by 49.9%, 49.0%, and 43.7% of subjects in the LNG-IUS12, LNG-IUS16, and LNG-IUS 20 groups. This increased to 82.0%, 81.0%, and 83.7% of subjects, respectively, by the end of the study.
LNG 20 IUS use in women with symptomatic endometriosis*

The LNG 20 IUS can:

- Reduce chronic pelvic pain associated with endometriosis
- Reduce dysmenorrhea
- Decrease the postoperative recurrence of endometriosis

* Not a licensed indication for LNG 20 IUS use

Ref. 1–5


Ref. 5 – A meta-analysis was performed in order to compare the efficacy of levonorgestrel releasing intrauterine system (LNG-IUS) with other treatments as a postoperative maintenance therapy for endometriosis in terms of pain reduction, recurrence prevention, side effects and patients’ satisfaction. Results: Among the 962 studies, 7 studies were selected: 7 studies included 4 randomized controlled trials with 212 patients, 1 prospective cohort study with 88 patients, and 2 retrospective studies with 191 patients. A meta-analysis showed that LNG-IUS was significantly effective in reducing pain after surgery (MD = 12.97, 95% confidence interval (CI): 5.55–20.39), with a comparable effect to gonadotropin-releasing hormone analogues (MD = 0.16, 95% CI: 2.02 to 1.70). LNG-IUS was also effective in decreasing the recurrence rate (RR = 0.40, 95% CI: 0.26–0.64), with an effect comparable to OC (OR = 1.00, 95% CI: 0.25–4.02) and danazol (RR = 0.30, 95% CI: 0.03–2.81). Furthermore, patients’ satisfaction with LNG-IUS was significantly higher than that with OC (OR = 8.60, 95% CI: 1.03–71.86). However, vaginal bleeding was significantly higher in the LNG-IUS group than in the gonadotropin-releasing hormone analogue group (RR = 27.0, 95% CI: 1.71–425.36). Conclusion: This meta-analysis found a positive effect of LNG-IUS as a postoperative maintenance therapy for endometriosis on pain relief, prevention of dysmenorrhea recurrence, and patients’ satisfaction.

Ref. 8 – In order to assess the safety and efficacy of LNG-IUS in the management of adenomyosis the search for the relevant studies which used LNG-IUS in management of patients with clinically or ultrasonographic diagnosed adenomyosis was performed. The main outcome measures were pain score at the end of follow-up, bleeding, symptomatic relief, uterine volume (mL), endometrial thickness (mm) and/or hemoglobin level. Results: Ten prospective studies (patients n = 551) were included. The overall effect estimates showed that the LNG-IUS led to significant reductions in pain score after 12 months (standardized mean difference [SMD] −3.87, 95% confidence interval [CI] −5.51 to −2.23, P < .001), 24 months (SMD −5.56, 95% CI −9.80 to −1.32, P = .01) and 36 months of insertion (SMD −3.81, 95% CI −4.27 to −3.36, P < .001). Similarly, the Pictorial Blood Assessment Chart (PBAC) showed significant reduction up to 36 months after LNG-IUS insertion (SMD −2.32, 95% CI −2.91 to −1.73, P < .001). The LNG-IUS led to significant reductions in the uterine volume 12 months (SMD −60, 95% CI −0.88 to −31, P < .001) and 36 months after insertion (SMD −0.42, 95% CI −0.69 to −0.14, P = .003). Conclusions: LNG-IUS is a promising and effective option for the management of adenomyosis. Its use effectively reduced the severity of symptoms, uterine volume and endometrial thickness, and improved laboratory outcomes.