APPLICATION FOR INCLUSION OF LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM FOR CONTRACEPTION IN THE 14th WHO MODEL LIST OF ESSENTIAL MEDICINES

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Application
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Background
Contraception is a truly valuable medical advance for women and society. There are different contraceptive methods, and the women’s choice and acceptance of them is likely to be affected by the efficacy, acceptability, tolerability and availability of alternatives and the desire not to conceive.

In the 1970s a new approach to the delivery of hormonal contraception was researched and developed. It was suggested that the addition of a progestogen to a non-medicated contraceptive device improved its contraceptive action\(^1\). Indeed, local levonorgestrel has a strong antiproliferative action on the endometrium. The endometrium becomes unresponsive to ovarian estrogens, although ovulation is usually not suppressed. This process is associated with progressive reduction of menstrual blood loss and menstrual duration\(^2\). The menstrual pattern and fertility return to normal soon after the levonorgestrel-releasing IUS is removed\(^3\). Among IUDs, levonorgestrel-releasing intrauterine system (LNG-IUS) has been used for reversible contraception. It has a T shaped plastic frame 32 mm long with a reservoir on the vertical stem of the IUS containing 52 mg of levonorgestrel mixed with polydimethylsiloxane. This allows a steady, local release of 20 microg levonorgestrel per day during the first year and 11 microg per day after 5 years with an average of 14 microg per day over 5 years. The LNG-releasing IUS should be installed during the first seven days of the cycle. Post-partum insertion can be done six weeks after normal delivery and twelve weeks after caesarean section. Insertion of the LNG-20 IUS may require local anaesthesia and dilatation of the cervical canal in nulliparous or perimenopausal woman. The net ingredient cost of the LNG-20 IUS is more expensive than copper bearing IUDs, however it offers non-contraceptive benefits particularly in women with heavy periods and may offer an alternative to hysterectomy.

About 145 million women are using Intrauterine Device (IUD) worldwide, which represents 14% of women in reproductive age. Generally, IUDs are the second most popular contraceptive method after sterilization\(^4\). LNG-releasing IUS is available in 47 countries\(^5\). LNG-IUS is registered in most European countries and the USA, as well as in increasing number of developing countries. Estimate of total...
patient exposure to date LNG-20 IUS has been available for 10 years in Europe and has been used by approximately two million women worldwide. LNG-IUS is used by approximately 1% of women aged 16-49 years in UK. In Latin America it was approved for use in Colombia, Peru and Uruguay. In Brazil, an IUS containing 52 mg of levonorgestrel received an official register renewal for new medicine through a National Health Surveillance Agency (ANVISA) resolution.

Aim of the search: To assess the effectiveness, acceptability and safety of levonorgestrel-releasing intrauterine system (LNG-IUS) in contraception and other clinical indications, in order to decide on its inclusion in the 14th WHO Model List of Essential Medicines.

Methods: A Medline search for systematic reviews and randomised controlled trials (RCTs), from 2000 to 2005, yielded two Cochrane systematic reviews, 16 RCTs and 71 all publication types, mainly revisions or non-controlled studies, some of them sponsored by the laboratory. The Cochrane systematic reviews compared IUSs versus other forms of reversible contraceptives as effective methods of preventing pregnancy and assessed their role for heavy menstrual bleeding. The RCTs mainly compared LNG-IUS to different strategies with respect to treatment in clinical indications other than contraception. Additionally a GFMER (The Geneva Foundation for Medical Education and Research) application document was reviewed.

Comments

EFFECTIVENESS

For contraception

Comparison to other reversible contraceptive methods

A Cochrane systematic review of eight RCTs assessed the contraceptive efficacy, tolerability and acceptability of hormonally impregnated intrauterine systems (IUSs) in comparison to other reversible contraceptive methods. It did not find randomized controlled trial comparing hormonally impregnated IUDs with oral, barrier or long-acting injectable contraceptives. But it identified four RCTs comparing LNG-20 IUSs with non-hormonal IUDs, one comparing the LNG-20 IUS with Norplant-2 and three comparing Progestasert with non-hormonal IUDs.

Hormonally impregnated IUS (LNG-20 IUS) compared with non-hormonal IUDs >250mm²

No significant difference was observed between the pregnancy rates for the LNG-20 users and those for the IUD >250mm² users at one year (1 trial; RR=1.05; 95%CI: 0.83-1.33) and for the fifth year of use (1 trial; RR=0.66; 95%CI: 0.25-1.75).

Hormonally impregnated IUS (LNG-20 IUS) compared with non-hormonal IUDs <=250mm²

Women using the LNG-20 IUS were significantly less likely to become pregnant than those using the copper IUD <=250mm², for the first (2 trials; RR=0.12; 95%CI: 0.03-0.49) and for the fifth year of use (2 trials; RR=0.08; 95%CI: 0.04 - 0.18).

Hormonally impregnated IUS (LNG-20 IUS) compared with subdermal implants (Norplant-2)
When the LNG-20 IUS was compared to Norplant-2, no significant differences were observed on efficacy.

Several articles have been published concerning pregnancy rates with levonorgestrel-releasing IUDs. A randomized multicenter (5 clinics) trial\textsuperscript{10} compared the use of LNG IUDs (n=1124) with TCu380Ag (n=1120) for seven years. Annual pregnancy rates for each IUD averaged 0.2/100 women whereas after 7 years of use, cumulative pregnancy rates were 1.1\% for the steroid-releasing IUD, and 1.4\% for the copper-releasing TCu380 IUD (not significant). Both IUDs proved highly acceptable and had few unanticipated side effects.

A randomized clinical trial\textsuperscript{11} evaluated LNG-IUS and copper-releasing intrauterine device (NovaT) inserted at the time of elective termination of pregnancy, duration no more than 12 weeks. The pregnancy rate at 5 years for the former treatment was significantly lower than the corresponding rate with NovaT (0.8 versus 9.5; $P<0.0004$). Special attention should be paid to the insertion procedure when carried out at the time of abortion. Both devices were well tolerated.

Another study\textsuperscript{12} reported no pregnancies during the follow-up of 12 years in 100 women originally fitted with the LNG-IUD.

\textbf{For noncontraceptive situations}

Hubacher and Grimes\textsuperscript{13} reviewed the noncontraceptive health benefits of intrauterine devices. The levonorgestrel intrauterine system can treat a variety of gynaecological disorders, including menorrhagia and anemia. The levonorgestrel system has also been used successfully as part of hormone replacement therapy, as adjuvant therapy with tamoxifen, and as an alternative to hysterectomy for women with bleeding problems.

\textbf{Endometriosis}

Dysmenorrhoea is the most frequent complaint reported by women with endometriosis. Laparoscopic surgery is often the treatment of choice for symptomatic disease, but results are not always satisfactory and pain recurrence is common. Moreover, most of the drugs used postoperatively, including danazol and GnRH agonists, cause subjective and metabolic side effects, are costly, and should generally be withdrawn after a few months.

A small non-randomised pilot study\textsuperscript{14} evaluated the effectiveness of LNG-IUS in rectovaginal endometriosis of eleven symptomatic patients over a 12-month follow-up. Dysmenorrhoea, pelvic pain, and deep dyspareunia greatly improved and the size of the endometriotic lesions was significantly reduced by treatment. Transrectal ultrasonography showed that the endometriotic nodules of the rectovaginal septum were reduced slightly but significantly in size after 6 months of therapy ($P<0.05$ vs. baseline values; paired $t$-test) and continued to become smaller in the following 6 months ($P<0.01$ for 12-month values vs. baseline values; paired $t$-test). Therapy with the LNG-IUS was associated with non-severe side effects in those patients.

Another study\textsuperscript{15} compared immediate LNG-IUS insertion versus expectant management after laparoscopic surgery for symptomatic endometriosis in 40 women. One year after surgery, moderate or severe dysmenorrhoea recurrence in subjects in the postoperative LNG-IUS group and in the surgery-only group was,
respectively, 10% vs. 45% ($P=0.03$, Fisher's exact test; $RR=0.22$; $95\% CI: 0.05–90$). Dyspareunia and nonmenstrual pain scores were also reduced to a greater extent with the postoperative use of LNG-IUS. A total of 75% women in the LNG-IUS group and 50% in the expectant management group were satisfied or very satisfied with the treatment received. At the 12-month evaluation, amenorrhoea was reported by five (28%) of the remaining 18 women in the LNG-IUD arm, hypomenorrhoea or spotting by nine (50%), and normal flows by four (22%).

**Idiopathic hypermenorrhoea**

LNG-IUS is more effective than no treatment for heavy menstrual bleeding. Although this device has not been compared to either placebo or no treatment control groups in randomised controlled trials, there is a 90% reduction from baseline in menstrual blood loss for the participants treated with it. In a Cochrane review\(^\text{16}\) of small RCTs with indirect measures LNG-IUS has been compared to oral cyclical norethisterone (NET) administered on days 5-26 in one trial and was significantly more effective although there was a large reduction from baseline in both groups and these differences were not perceived by the women undergoing the treatment. The LNG-IUS was not as effective as transcervical resection of the endometrium (TCRE), a surgical procedure, in two trials.

The LNG-IUS is associated with a higher rate of intermenstrual bleeding and breast tenderness than NET and also a higher rate of progestogenic side effects than TCRE, but rates of dysmenorrhoea do not appear to differ. The adverse side effects may lead to premature removal of the dispositive, hence reducing its cost-effectiveness. Three trials have reported expulsion of the device within 12 months of 3.3%, 4.6% and 5.9% of patients.

The LNG-IUS was more acceptable as a treatment for heavy menstrual bleeding than NET and women in the former group were willing to continue with their treatment when compared with the NET group (77% vs. 22%). In contrast, there were no differences in satisfaction rate when it is compared with TCRE (IUS 85% vs. TCRE 94%). There was no conclusive evidence of changes in quality of life between groups.

Some caution must be exercised in the interpretation of results in this meta-analysis, since, in most cases, those are based on only one small trial.

Two RCTs\(^\text{17,18}\) compared the effectiveness of endometrial thermal balloon ablation and the levonorgestrel intrauterine system (LNG-IUS) in the management of menorrhagia. Both methods are equally effective in both studies. In the second one, after one year of follow-up, the medicated device was less effective than thermal balloon ablation in reducing the menstrual blood loss.

Another study\(^\text{19}\) assessed the effects of copper intrauterine device (Cu-IUD) and progesterone (PRG-IUS) or levonorgestrel (LNG-IUS) releasing intrauterine systems on menstrual bleeding, menorrhagia and dysfunctional uterine bleeding in a one-year follow-up. PRG-IUS and LNG-IUS significantly reduced menstrual blood loss and irregular bleeding. In contrast, this did not occur with the insertion of Cu-IUDs.

Levonorgestrel-releasing intrauterine system was compared to hysterectomy in the treatment of essential menorrhagia\(^\text{20}\). After 5 years of follow-up, treatment with
LNG-IUS seems a reversible alternative to hysterectomy for women who perceive their menstrual blood levels as heavy. A prospective controlled trial assessed the efficacy of LNG-IUS in myoma-related menorrhagia. Following LNG-IUD insertion, statistically significant decreases in menstrual blood flow and increases in hemoglobin values were noted. In contrast, in an open observational study the effectiveness of a levonorgestrel-releasing intrauterine device (LNG-IUD) in the treatment of myoma-related menorrhagia was not evidenced.

ACCEPTABILITY

LNG-20 users were more likely than all the copper IUD users to discontinue treatment because of hormonal side effects (one trial; RR= 4.24; 95% CI: 1.99-9.05 for IUD>250 mm² at 5 years; one trial; RR=5.18; 95%CI: 1.32-20.34 for IUD =/=<250 mm² at 5 years), and menstrual disturbance (one trial; RR=1.48; 95%CI: 1.23-1.79 for IUD>250 mm² at 5 years), which on further breakdown of the data was due to amenorrhoea. Diaz and associates evaluated the possibility of using LNG-IUS in women with increased bleeding wanting an IUD and in copper IUD users requesting removal of the device for bleeding problems. A total of 256 women chose LNG-IUS and were accepted into the study during the enrollment period. This represents 23.3% of all new acceptors of contraceptive methods in the clinic during the same period. Comparing the performance in the group of women who chose the LNG-IUS as a first option with those having heavy bleeding, the only difference found was a higher expulsion rate in the group with bleeding problems.

SAFETY

According GFMER application, the LNG-IUS complications are rare and are described as perforation during insertion, expulsion or infection. The most common side effects are bleeding irregularities, acne, oily skin, breast tenderness, nausea, mood changes, and headache. The application mentioned contra-indications of LNG-IUS such as ongoing pregnancy, women being less than four weeks postpartum or immediate post-abortion, post septic abortion, cancer of the cervix and uterus, breast cancer, anatomical abnormalities distorting the uterine cavity, pelvic inflammatory disease (PID) – current or within the last 3 months, pelvic tuberculosis, unexplained uterine bleeding, postpartum endometritis, acute hepatic affections and liver tumor, severe liver cirrhosis, thromboembolic diseases, coagulation disorders or use of anticoagulant medicines, severe anemia, immunosuppressive therapy, multiple sexual partners, hypersensitivity to levonorgestrel or to another component of the device. Most common side effects include menstrual changes (reduction of blood loss, amenorrhoea, prolonged spotting), lower abdominal pain, acne or other skin problems, back pain, mastalgia, headache, vaginal discharge, mood changes and nausea. The first months of use are often characterised by irregular, scanty bleeding, which in most cases resolves spontaneously. Uncommon complications can be: expulsion of the device, perforation during insertion and pregnancy. The risk of pelvic inflammatory disease is reduced, because of reduced menstrual blood loss, endometrial suppression, and thickening of the cervical mucus.
In a Cochrane review\(^1\), LNG-20 IUS compared with copper IUDs >250mm\(^2\) induced more amenorrhoea and device expulsion. Amenorrhoea risk increased over time (at three months: RR= 2.25; 95%CI: 1.36-3.56; at three years follow-up: RR= 7.24; 95%CI: 4.14 - 12.55). No significant differences were noticed in terms of prolonged bleeding. Other menstrual disturbance outcomes were not identified, but in one study LNG-20 IUS users experienced significantly less dysmenorrhoea. No data were collected for hormonal side effects. LNG-20 IUS versus Norplant-2 users experienced significantly more amenorrhoea at a one-year follow-up (RR= 2.27, 95%CI: 1.03-4.99), at a two-years follow-up (RR =42.46; 95%CI: 2.62-689.20) and at a three-years follow-up (2.65; 95%CI: 0.53-13.20). They were also experienced more oligomenorrhoea at a two-years follow-up, but significant differences were not found in the other periods\(^1\).

In a comparison\(^23\) between LNG IUD and TCu380Ag for prolonged use, LNG-IUS significantly decreased bleeding and spotting days in comparison with the copper-mediated IUD. Dysmenorrhoea, vaginitis, and myoma in women with the levonorgestrel IUD were markedly decreased in comparison with the experience of copper IUD users. Significantly higher rates of amenorrhoea, delayed ovarian follicular atresia, skin and hair conditions, and headache were observed with the steroid IUD versus the copper-releasing IUD. Rates of reported adverse effects for either IUD were highest in the first 2 years of use and among women under age 25.

In a retrospective cohort\(^24\) investigating the complications of the intrauterine device in 129 nulliparous and 332 parous women, rates of expulsion for the LNG-IUS were 0 to 0.2% per year versus 0 to 1.2% per year in users of copper IUDs. Nulliparous women did not show more complications than parous women.

A RCT\(^25\) compared the safety and acceptability of LNG-IUS to oral contraceptives (OCs) in 193 young nulliparous women. The one-year continuation rates were 79.8% and 72.7%, respectively \((P = 0.28)\). The most common reason (31%) for discontinuation in the IUS group was pain. The most common adverse events reported during the study period were abdominal pain and headache. In the OC group, hormonal side effects were the predominant medical reason for study termination. The safety and acceptability of the LNG-IUS for contraception was observed to be as good as OCs, with a high continuation rate.

Pregnancy with the LNG IUS in situ is rare. Ectopic pregnancies constitute 53% of all pregnancies. Typical pregnancy symptoms occur during pregnancies with the LNG IUS. The importance to counsel about the risk of pregnancy before insertion is highlighted\(^26\). In another study\(^27\), by the end of 5 years, there were 2 pregnancies in TCu 380A group, but none in LNG-IUS group. There were 24 amenorrhoea cases in LNG-IUS users. Oligomenorrhoea and amenorrhoea caused by the local effects of LNG were reversible and did no harm to women's health.

**COST**

LNG-IUS is generally more expensive compared to copper IUDs. Comparative cost-effectiveness is influenced by the duration of the insertion. The levonorgestrel-releasing intrauterine system is licensed as effective for five years and compared to other medical therapies is much cheaper over 5 years although it becomes expensive if the device is removed before that time limit\(^16\).
A randomized controlled trial\textsuperscript{28} compared outcomes, quality-of-life issues, and costs of the LNG-IUS vs. hysterectomy in the treatment of menorrhagia. After five years of follow-up, the discounted direct and indirect costs in the LNG-IUS group (2,817 USD; 95\%CI: 2,222 USD-3,530 USD per participant) remained substantially lower than in the hysterectomy group (4,660 USD; 95\%CI: 4,014 USD-5,180 USD). In an economic analysis\textsuperscript{29} of nine contraceptive methods for women in the United States, the least expensive methods (accounting for all costs) were LNG-20 IUS, copper T 380A IUD and 3-month injectable contraceptive. The 5-year cost/person were 1,646 USD, 1,678 USD and 2,195 USD, respectively.

**Conclusion**

**For contraception:**

1) LNG-20 IUS is as effective as IUD >250mm\textsuperscript{2} and subdermal Norplant-2.
2) LNG-20 IUS discontinuation treatment rate is similar to Norplant-2, but significantly higher than all the copper IUDs. Amenorrhoea is the main reason for the LNG-20 IUS discontinuation.
3) LNG-20 IUS most common side effects include menstrual and hormonal changes. LNG-20 IUS is more likely to induce amenorrhoea than copper IUDs >250mm\textsuperscript{2} and Norplant-2, and that risk increased over time. LNG-20 IUS expulsion rate is higher in relation to copper IUDs >250mm\textsuperscript{2}.
4) LNG-20 IUS and copper T 380A IUD insertions are the least expensive contraceptive methods (accounting for all costs), corresponding to a 5-year cost/person of 1,646 USD and 1,678 USD, respectively.

**For non-contraceptive purposes**

LNG-20 IUS insertion is safer, more effective and more cost-effective for endometriosis and essential menorrhagia in comparison to other treatments.

**Recommendation**

Even with no discernible difference in terms of contraceptive effectiveness when compared to IUDs >250mm\textsuperscript{2} or Norplant-2, LNG-20 IUS is an alternative in those women who are concerned about menstrual bleeding and pain with IUD use. It has acceptable and reversible side effects, except for amenorrhoea that increases with time of use and contributed to discontinuation treatment. Additionally this hormone-releasing system evidences effectiveness, safety and cost-effectiveness in non-contraceptive disorders (endometriosis, essential menorrhagia). It seems better than other methods of treatment. Regarding essential medicines definition, this second aspect seems to me a stronger reason for its inclusion in the 14\textsuperscript{th} WHO EDL.

**References**

4. WHO. The intrauterine device (IUD) – worth singing about. *Progress in Reproductive Health Research* 2002, n°60, p. 3


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