Levonorgestrel-releasing intrauterine device used for dysmenorrhea: five-year literature review

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Summary

Intrauterine devices (IUDs) provide highly effective, long-term, safe, reversible contraception, and are the most widely used reversible contraceptive method worldwide. The levonorgestrel-releasing IUD (LNG-IUD), originally designed for long-term contraceptives, is now recognized to provide non-contraceptive health benefits. These include severe dysmenorrhea and/or heavy menstrual bleeding associated with uterine myoma, endometriosis, and adenomyosis. This report aims to review the last five-year literature on the efficacy and safety of the LNG-IUD in women with dysmenorrhea. Dysmenorrhea has been reported to decrease in all women. LNG-IUD seems to be superior over copper-releasing IUD for improving dysmenorrhea. The LNG-IUD is beneficial for symptom recurrence and endometriotic cyst recurrence after conservative surgery for patients with severe pain related to endometriosis. There is also evidence to support its role in menstrual problems of severely obese adolescent females. Expulsion, one of the important factors for IUD acceptability, is rare but more common in women with distorted uterine cavity. In the treatment of dysmenorrhea, the LNG-IUD is equal or superior to treat with systemic progestins or oral contraceptives even in adolescent or menopausal women.

Key words: Intrauterine device; Dysmenorrhea; Levonorgestrel-releasing intrauterine device (LNG-IUD); Adenomyosis; endometriosis.

Introduction

Intrauterine hormone delivery for contraception began with the invention of the progesterone-releasing intrauterine system in 1970 and this was soon followed by the much more effective and longer acting levonorgestrel-releasing intrauterine device (LNG-IUD) [1-5]. Non-contraceptive health benefits are now recognized as an important aspect of the overall impact of all hormonal contraceptives [6-9]. The LNG-IUD is particularly effective at producing a number of health benefits for women using the LNG-IUD as a contraceptive (reduced menstrual bleeding, reduced dysmenorrhea, and the potential for prevention of a number of gynecological conditions in the longer term, such as iron-deficient anemia, endometrial hyperplasia, adenomyosis, endometriosis, and perhaps others) [7, 10-14]. The device has received approval for indications other than contraception, such as the treatment of menorrhagia and protection of the endometrium during estrogen therapy in postmenopause in many countries [7, 10-12].

The LNG-IUD expulsion, which results in failure of contraception and/or failed relief from symptoms, may be experienced more often among patients with uterine cavity distortion [15-17]. The LNG-IUD is commonly positioned incorrectly in these patients and can be easily flushed out by heavy menstrual flow. This report attempted to review the literature, published within the last five years, regarding LNG-IUD indications for dysmenorrhea and its expulsion as a prognostic factor for safe and effective acceptability.

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Materials and Methods

A PubMed search (up to December 2012) was conducted with the following search terms: [levonorgestrel-releasing intrauterine device] and [dysmenorrhea], limited to English language papers only, published within the last five years. The authors did not consider abstracts of conference presentation and dissertations. This search resulted in 18 articles (including six reviews). These papers were manually searched and the most relevant articles were included in this review. Publications reporting single case of small case series were not considered to represent sufficiently robust evidence and were excluded.

Results

Table 1 summarized the seven studies identified in which LNG-IUD was used as a therapy for dysmenorrhea and its subsequent expulsion. The recent prospective randomized study by Kekekci *et al*. [18] compared LNG-IUD and copper-releasing IUD, in women with adenomyosis-associated dysmenorrheal for 12 months. The LNG-IUS significantly improved the duration of menstrual bleeding, dysmenorrhea, and hemoglobin levels at the first and 12th month of the treatment in both groups. Moreover, LNG-IUD had similar efficacy but significantly lower side-effects when compared to copper-releasing IUD.

Shen *et al*. [19] evaluated the efficacy and side-effects of the LNG-IUD in the treatment of moderate or severe dysmenorrhea associated with adenomyosis for a three-year follow-up period. The visual analog scale (VAS) of dysmenorrhea dropped continuously and significantly from the baseline score of 77.9 ± 14.7 to 11.8 ± 17.9 after 36 months of the LNG-IUS insertion. Of 94, 17 prema-

Table 1. — *Last five-years studies on the LNG-IUD use in dysmenorrhea.*

Methodology	Findings and proposal
Prospective RCT for LNG-IUD vs. intrauterine copper device, in women with adenomyosis-associated symptoms, with 12-month follow-up.	Similar and significant improvement with both treatments. Side-effects lower in the LNG-IUD group. No expulsion occurred. [18]
Prospective study for the efficacy of LNG-IUD in women with adenomyosis-associated symptoms, with 36-month follow-up.	Of 94, 17 premature removals and 15 expulsions occurred within a three-year period. At 36 months, the overall satisfaction rate was 72.5 % [19].
A double-blind RCT for pelvic endometriosis-related pain after laparoscopic conservative surgery, with 12-month follow-up.	LNG-IUD group had greater reduction in dysmenorrhea VAS and pelvic pain VAS, but a comparable reduction in dyspareunia VAS. No expulsion occurred [20]
Retrospective analysis of the efficacy of LNG-IUD in perimenopausal women with dysmenorrhea for 12 months.	Twenty-six of 192 (13.5%) women failed with LNG-IUS treatment receiving hysterectomy. No expulsion occurred [21].
Cohort study of adolescent females with menstrual problems who underwent bariatric surgery over a two-year period.	Ninety-two percent of patients underwent LNG-IUD placement. One of 25 experienced unanticipated expulsion [22].
Retrospective study of the efficacy and safety of LNG-IUD for adenomyosis-related menorrhagia and/or dysmenorrhea, with seven-year follow-up.	Expulsion occurred in 25.3% with the conventional method, during seven-year follow-up. Dysmenorrhea greatly improved [15].
Prospective clinical trial to quantify the LNG-IUD - induced subendometrial blood flow.	Increased subendometrial blood flow in patients with severe dysmenorrheal after controlling for IUD. No expulsion occurred [24].

VAS: visual analog scale.

ture removals and 15 expulsions occurred within the three-year period.

Endometriosis is a disease that is less likely to be cure by conservative surgery. Postoperative measures are needed to prevent the recurrence of disease. Tanmahasamut *et al.* [20] followed up 55 women operated for deep infiltrating endometriosis using LNG-IUD. Compared with the control group, the LNG-IUD group had greater reduction in VAS and pelvic pain VAS but a comparable reduction in dyspareunia VAS. Two patients in LNG-IUD group (7.4%) and nine in the expectant management group (39.1%) had recurrent dysmenorrhea within one year postoperatively. Number-needed-to-treat to prevent one case with recurrent dysmenorrhea within the first year was three cases. The LNG-IUD may be effective and well accepted for long-term therapy after conservative surgery for patients with moderate to severe pain related to endometriosis.

Yoo *et al.* [21] retrospectively analyzed 192 women over 40-years-old for a two-year follow-up period on the changes in the amount and duration of bleeding and the pain scores for 24 months. Twenty-six (13.5%) women failed with LNG-IUD treatment and they received hysterectomy. When hysterectomy was performed, the average duration from LNG-IUD insertion to hysterectomy was 8.9 months. The participants who persisted with the LNG-IUD treatment for 24 months showed a success rate of 80.7%. They proposed that insufficient reduction of pain score during the first three months and menstrual blood loss during the first six months after insertion of the LNG-IUD are important factors that affect undergoing hysterectomy.

With the increasing prevalence of severe obesity during adolescence comes an increase in relevant obesity-related comorbidities and obesity-related menstrual concerns. A recent cohort study evaluated the prevalence of menstrual problems including dysmenorrhea and related medical comorbidities, and the acceptance rate of the LNG-IUD placed at the time of bariatric surgery among a sample of severely obese adolescents [22]. There is a high prevalence of menstrual problems, and the majority accepted the LNG-IUD, indicating it is a viable option among this population.

Because adenomyosis is usually associated with an enlarged uterus, uterine distortion of great retroflexed/anteflexed uterine curvature, LNG-IUD is commonly positioned incorrectly in these patients and can be easily flushed out by the menstrual flow [23]. In addition, low positioning or partial expulsion of IUD may be related to a longer period of spotting and bleeding. Peng *et al.* [15] compared a novel insertion technique and conventional technique to overcome this problem. Expulsion occurs in 25.3% of patients with the conventional method, compared with 10.2% of patients with their novel method [15]. Hemoglobin levels and dysmenorrhea improve greatly in both groups after LNG-IUD insertion.

LNG-IUD induces some bleeding disturbances including unexpected breakthrough bleeding, which is an important reason for discontinuation [7, 10-12]. Jiménez *et al.* [24] compared the subendometrial microvascularization and uterine artery blood flow in LNG-IUD and copper-releasing IUD. There is an increased subendometrial blood flow in patients with severe dysmenorrhea and/or bleeding, after controlling for both IUD types. The results provide new data on the bleeding patterns related to these IUD types that may be relevant during contraception use.

Discussion

The use of LNG-IUD is an alternative for the medical treatment of adolescent to perimenopausal women suffering from dysmenorrhea. For women who do not wish to become pregnant, this device offers the possibility of at least five years of treatment following one single intervention. Most users experience a dramatic reduction in menstrual bleeding, and about 15% to 20% of women become amenorrheic one year after insertion [1, 2, 7, 10-12]. The device's strong local effects on the endometrium benefit women with various benign gynecological conditions such as menorrhagia, dysmenorrhea, leiomyomata, adenomyosis, and endometriosis [1, 2, 7, 10-12]. There is also evidence to support its role in endometrial protection during postmenopausal estrogen replacement therapy, and in the treatment of endometrial hyperplasia. When compared to gonadotropin-releasing hormone (GnRH) analogues or depot progestins, treatment with the LNG-IUD has resulted in favorable and similar symptom control. As with a GnRH analogue [25], a rapid therapeutic effect of the LNG-IUD is seen among those responding to the therapies. The follow-up of the initial study by Petta *et al*. [26] was extended up to five to seven years [15, 19]. Of the women still using the LNG-IUD at that time, the majority (78%) displays VAS scores of between 0 and 3 [15, 18-22]. Thus, among women responding, the LNG-IUD offers a safe and long-term therapeutic option for women suffering from endometriosis-related pelvic pain.

Problems with LNG-IUD insertion are often encountered in routine clinical practice among patients with adenomyosis; the LNG-IUD insertion was reported to be more difficult and painful than insertion of the copper device [15, 27], possibly because of its more rigid and broader insertion tube [28]. Expulsion is more common in women with adenomyosis [2]. The uterine cavity of women with adenomyosis is sometimes large and distorted by anteflexion or retroflexion. This abnormal anatomy may lead to IUD placement in the lower uterine cavity. A significant higher expulsion rate and prolonged spotting are noted with a LNG-IUD situated in the cervical canal, compared with an IUD in the uterine cavity [29]. These factors may further hinder the insertion of LNG-IUD and lead to incorrect positioning, which is a risk factor for expulsion [16]. This could partially explain why LNG-IUD has a higher expulsion rate than copper-releasing device (about 4.9%) in therapy for menorrhagia [17]. Frequent confirmation by ultrasound may be required in patients with severe adenomyosis and distorted uterus. As Peng *et al.* [15] proposed, consideration should also be given to the difference in size between LNG-IUD and that of some uterine cavities in patients with adenomyosis; a standard-sized IUD may not be optimal in patients with heavy menstrual bleeding. It is possible that a variety of sizes of IUD may be required in the future.

The local endometrial effect has been studied in several endometrial biopsies from LNG-IUD users, and there is a significant change in endometrial vascularization, and demonstrated by a decrease in the mean vascular density and an increase in mean vessel area, suggesting an endometrial effect [30-33]. This is an important reason for LNG-IUD discontinuation [24]. Jiménez *et al.* [24] demonstrated that there is a significant increase in subendometrial blood flow in patients who presented with IUD-related side-effects (severe dysmenorrhea and/or bleeding).

Although the LNG-IUD is an excellent method, the possibility of failure and hormonal side-effects exists, and in some women extensive bleeding cannot be controlled. Expulsions are rare but may be followed by therapeutic failure and are more common in women with a distorted uterine cavity. Counseling prior to insertion and during use is mandatory to avoid premature discontinuation and must make reference to the few hormonal side-effects and expected bleeding patterns.

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