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Review Article

Levonorgestrel Intrauterine System Mirena : An Update

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Abstract

Mirena is a levonorgestrel-releasing intrauterine system. Apart from being a reliable contraception, Mirena is now widely indicated for its non contraceptive benefits which include treatment of menorrhagia, dysmenorrhoea, premenstrual symptoms, fibroids, adenomyosis, endometriosis etc. It is now used even for hormone replacement therapy. This review article tries to explore different aspects of Mirena for treatment of menorrhagia compared to other available methods based on recent trials.

Introduction

Mirena is a new intrauterine hormonal contraceptive system releasing levonorgestrel. It has been available worldwide since 1995 and more than 6 million women worldwide have used it for contraception[1]. The levonorgestrel-releasing intrauterine system (IUS) Mirena is a long-acting, fully reversible method of contraception. It is one of the most effective forms of contraception available, and combines the advantages of both hormonal and intrauterine contraception. Mirena also gives the users many non-contraceptive benefits: the amount of menstrual bleeding and the number of days of menstrual bleeding are reduced, which makes it suitable for the treatment of menorrhagia. Dysmenorrhoea and premenstrual symptoms are also relieved. It is now used for therapeutic benefits in fibroids, adenomyosis and endometriosis. In addition, Mirena provides protection for the endometrium during hormone replacement therapy. The local release of levonorgestrel into the uterine cavity results in a strong uniform suppression of the endometrial epithelium as the epithelium becomes insensitive to estradiol released from the ovaries. This accounts for the reduction in menstrual blood loss. All possible patterns of bleeding are seen among users of the Mirena; however, most of the women who experience total amenorrhoea continue to ovulate. The first months of use are often characterized by irregular, scanty bleeding, which in most cases resolves spontaneously. The menstrual pattern and fertility return to normal soon after the levonorgestrel-releasing IUS Mirena is removed. The contraceptive efficacy is high with 5-year failure rates of 0.5-1.1 per 100 users[2]. The absolute number of ectopic pregnancies at 5 years is around 0.02 per 100 women years[1]. Mirena is equally effective in all age groups and the bodyweight of the user is not associated with failure of the method. In Western cultures continuance rates among users of Mirena are comparable with those of other long-term methods of contraception. Premature removal of the device is most often associated with heavy menstrual bleeding and pain, as with other long-term methods of contraception, and is most common in the youngest age group. When adequately counseled about the benign nature of oligo- or amenorrhoea, most women are very willing to accept life without menstruation. The risk of premature removal can be markedly diminished with good pre-insertion counseling, which also markedly increases user satisfaction. User satisfaction is strongly associated with the information given at the time of the levonorgestrel-releasing IUS insertion.

Types of IntraUterine Systems

Progestasert was the first hormonal uterine device, developed in 1976 and manufactured until 2001. It contained progesterone that was released at a rate of 65 micrograms per day. In most countries it was replaced annually, though it was approved for 18 months of use in France. It had a failure rate of 2% per year.

Development and studies of the Mirena Coil began in the 1970s. Schering Health distributes Mirena outside

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the United States, while Berlex distributes it inside the United States. Mirena was first marketed commercially in Finland in 1990, but not approved by the U.S. Food and Drug Administration until 2000.

Contrel, the Belgian company that developed the frameless GyneFix IUD, is developing a lower-dose (14 micrograms levonorgestrel per day) T-frame IUS named Femilis. Femilis would come in a smaller size (Femilis Slim) for nulliparous women. It would be inserted without a plunger, and it is hoped its performance would be less dependent on the experience of the health care professional.

Several trials with positive results have been done on a frameless IUS called FibroPlant-LNG (also from Contrel). FibroPlant is anchored to the fundus of the uterus rather than being held in by a frame.

Drug Description

MIRENA® (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body[3].

Mirena is recommended for women who have had at least one child, are in a stable, mutually monogamous relationship, have no history of pelvic inflammatory disease, and have no history of ectopic pregnancy or condition that would predispose to ectopic pregnancy. Mirena® does not protect against HIV or STDs.

Mirena contains 52 mg of levonorgestrel. Initially, levonorgestrel is released at a rate of approximately 20 µg/day. This rate decreases progressively to half that value after 5 years[3].

Mirena is indicated for intrauterine contraception and for other purposes for up to 5 years. Thereafter, if continued contraception is desired, the system should be replaced.

The Food and Drug Administration approved this method in December 2000[4]. In clinical studies, the most common side effects with Mirena® included:

- Menstrual changes
- Lower abdominal pain (cramps)
- Acne or other skin problems
- Back pain
- Breast tenderness
- Headache
- Mood changes
- Nausea

Ovarian cysts have been diagnosed in about 12% of Mirena users[4]. In most cases, these cysts disappeared spontaneously during 2 to 3 months' observation. Women who have, or have had, breast cancer should not use hormonal therapy.

Long-term effects and congenital anomalies[3]

When pregnancy continues with Mirena in place, long-term effects on the offspring are unknown. Because of the intrauterine administration of levonorgestrel and local exposure to the hormone, the possibility of teratogenicity following exposure to Mirena, especially virilization, cannot be completely excluded. Clinical experience with the outcomes of pregnancies is limited due to the small number of reported pregnancies following exposure to Mirena.

Congenital anomalies have occurred infrequently when Mirena has been in place during pregnancy. In these cases the role of Mirena in the development of the congenital anomalies is unknown. As of September 1999, 32 live births following exposure to Mirena were reported retrospectively. All but 2 of the infants were healthy at birth. One infant had pulmonary artery hypoplasia and another infant had cystic hypoplastic kidneys. (A sibling of this infant had renal agenesis with no Mirena exposure.)

The Cochrane Database Systemic Review. 2005 on LNG-IUS[5]

Objective: To determine the effectiveness and acceptability of progesterone or progestogen-releasing intrauterine devices in achieving a reduction in heavy menstrual bleeding.

Studies which might describe randomized controlled trials of progesterone or progestogen-releasing intrauterine devices for the treatment of heavy menstrual bleeding were obtained by electronic searches of The Cochrane Library, MEDLINE (1966 to 2005) and EMBASE (1980 to 2005). Companies producing progestogen-releasing intrauterine devices

and experts in the field were contacted for information on published and unpublished trials. Randomized controlled trials in women of reproductive age treated with progesterone or progestogen-releasing intrauterine devices versus no treatment, placebo, or other medical or surgical therapy for heavy menstrual bleeding within primary care, family planning or specialist clinic settings were eligible for inclusion. Women with postmenopausal bleeding, intermenstrual or irregular bleeding, or pathological causes of heavy menstrual bleeding were excluded. Potential trials were independently assessed by three review authors and nine trials met the criteria for inclusion in the review. The reviewers extracted the data independently and data were pooled where appropriate. Odds ratios (OR) were estimated from the data for dichotomous outcomes and weighted mean differences (WMD) for continuous outcomes. The primary outcome was reduction in menstrual blood loss but incidence of side effects, changes in quality of life, satisfaction and acceptability measures were also assessed.

Results:

The levonorgestrel-releasing intrauterine device (LNG IUS) has been compared to oral cyclical norethisterone (NET) administered on days 5 to 26 of the menstrual cycle in one trial and was significantly more effective although there was a large reduction in loss from baseline in both groups. Some short term side effects were more common in the LNG IUS group but a significantly greater proportion of women in this group were satisfied and willing to continue with their treatment. In one trial of women awaiting hysterectomy, where the LNG IUS was compared with a control group taking their existing medical therapy, a higher proportion of the women in the intrauterine device group cancelled their planned surgery after six months of treatment.The LNG IUS has been compared to an endometrial ablation: either transcervical resection of the endometrium (TCRE) (two trials) or balloon ablation (three trials). There was a significantly greater mean reduction in menstrual bleeding in one trial in those undergoing balloon ablation (WMD -45.2 units, 95% CI -56.9 to -33.5), a lower score on the pictorial blood loss chart (PBAC) (WMD 33.2 units, 95% CI 27.2 to 39.2) and higher rates of successful treatment in 3 trials including both balloon and TCRE (OR 0.28, 95% CI 0.14 to 0.58) but the rates of satisfaction with treatment were similar. There was no conclusive evidence of changes in quality of life between groups but women with the LNG IUS had a greater incidence of progestogenic side effects within one year. The LNG IUS has been compared to hysterectomy in one trial. There was no evidence of a change in quality of life scores but the LNG IUS treatment had lower costs than with hysterectomy, both at one and five-years follow up.

Conclusions of cochrane: The levonorgestrel-releasing intrauterine device (LNG IUS) is more effective than cyclical norethisterone (for 21 days) as a treatment for heavy menstrual bleeding. Women with an LNG IUS are more satisfied and willing to continue with treatment but experience more side effects, such as intermenstrual bleeding and breast tenderness.The LNG IUS results in a smaller mean reduction in menstrual blood loss (as assessed by the PBAC chart) than endometrial ablation but there is no evidence of a difference in the rate of satisfaction with treatment. Women with an LNG IUS experience more progestogenic side effects compared to women having TCRE for treatment of their heavy menstrual bleeding but there is no evidence of a difference in their perceived quality of life.The LNG IUS treatment costs less than hysterectomy but there is no evidence of a difference in quality of life measures between these groups.There are no data available from randomised controlled trials comparing progesterone-releasing intrauterine systems to either placebo or other commonly used medical therapies for heavy menstrual bleeding.

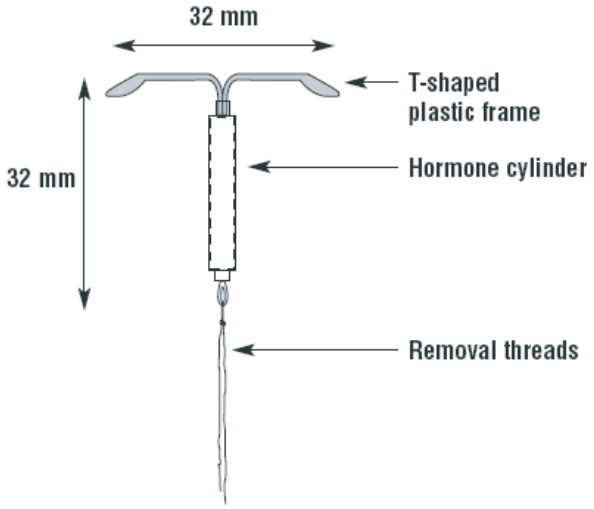

Fig. : *Mirena*

Cochrane Database Syst Rev. 2006[6]

Surgery versus medical therapy for heavy menstrual bleeding(HMB).

To compare the effectiveness, safety and acceptability of surgery versus medical therapy for HMB, the Cochrane Menstrual Disorders and Subfertility Group trials register Cochrane Controlled Trials Register (The Cochrane Library Issue 3, 2005), MEDLINE EMBASE, Current Contents, Biological Abstracts, PsycINFO, and CINAHL were searched. The eight included trials randomised 821 women. In comparisons of oral medication versus surgery, 58% of women randomised to medical treatment had received surgery by two years. Compared to oral medication, endometrial resection was significantly more effective in controlling bleeding (at four months: OR 10.62, 95% CI 5.30 to 21.27) and significantly less likely to cause side effects (at four months: OR 0.15, 95% CI 0.07 to 0.31) and hysterectomy resulted in significantly greater improvements in mental health (at six months p = 0.04). In comparisons of LNG-IUS versus conservative surgery or hysterectomy, at one year there was no statistically significant difference in satisfaction rates or quality of life, though adverse effects were significantly less likely with conservative surgery (OR 0.24, 95% CI 0.11 to 0.49). Two trials found conservative surgery significantly more effective than LNG-IUS in controlling bleeding at one year (OR 3.99, 95% CI 1.53 to 10.38).

Conclusions: Surgery, especially hysterectomy, reduces menstrual bleeding at one year more than medical treatments but LNG-IUS appears equally effective in improving quality of life. The evidence for longer term comparisons is weak and inconsistent. Oral medication suits a minority of women long term.

Recent other studies on LNG-IUS Mirena

In a prospective-observational study of 225 women who had a LNG-IUS inserted for control of idiopathic menorrhagia, there was a statistically significant reduction in the amount of bleeding, an increase of haemoglobin and ferritin levels, and an improved quality of life (QoL) score[7]. A high degree of satisfaction was reported by over 98% of patients. So it seems that the LNG-IUS is an effective and well-tolerated treatment modality in idiopathic menorrhagia. The QoL of women treated with the LNG-IUS is markedly improved, causing high levels of patient satisfaction. This IUS can be therefore be regarded as a first-choice therapy in idiopathic menorrhagia[7].

A randomized controlled trial on the effects of LNG-IUD and a gonadotropin-releasing hormone agonist (GnRHa) on uterine volume, uterine arteries pulsatility index (PI) and endometrial thickness before and after six months of endometriosis treatment[8] compared on Sixty women aged 18-40 years showed that the levonorgestrel released directly on to the endometrium by the LNG-IUD induced smaller uterine changes than did the hypoestrogenism induced by GnRHa. Nevertheless, both promoted similar effects on endometrial thickness[8].

LNG-IUS Mirena is associated with high contraceptive efficacy, an improvement in menstrual blood loss in women with idiopathic menorrhagia, menorrhagia due to thrombophilic diseases and fibroids, and an excellent endometrial protection during postmenopausal estrogen therapy[9]. Moreover, the device is able to reduce pelvic pain and dysmenorrhea as well as improve the staging of endometriosis and adenomyosis, and to control, albeit partially, endometrial hyperplasia. The expectation is that in years to come the number of hysterectomies and female sterilizations will fall due to increased use of the device, including use by patients with endometriosis and HIV-positive women. It would also be desirable to develop a smaller device for postmenopausal women and nulligravidas[9].

The efficacy of LNG-IUS was proved superior to both oral and intramuscular medroxyprogesterone acetate in the treatment of perimenopausal menorrhagia[10,11].

LNG-IUS Mirena is an effective and well-accepted option overall for the medical management of menorrhagia[12]. In a prospective, open, nonrandomized clinical trial menorrhagia was cured in as high as (77.7%) 45 patients at 3 months and in all patients at 36 months[12]. The most common side effect was intermenstrual spotting during the first 6 months, and 18 patients (28.57%) developed amenorrhea.

A prospective study involving 50 women recruited from a district general hospital in South Wales indicated that the levonorgestrel-releasing intrauterine system (LNG-IUS) represents an effective nonsurgical treatment for menorrhagia and dysmenorrhea[13]. Treatment for menorrhagia with a combination of prostaglandin synthetase inhibitors and antifibrinolytic drugs had failed in these women, and they were on a waiting list for hysterectomy or transcervical resection of the endometrium. Menstrual loss was estimated using a modified pictorial chart and the full blood count

and ferritin were measured preinsertion and at 3 and 6-9 months postinsertion. The device was spontaneously expelled in 6 women and almost all subjects experienced some unscheduled bleeding during the first 6-8 weeks postinsertion. Of the 42 women who attended the 3-month visit, 37 were satisfied with the results of the LNG-IUS device and wished to continue; only 5 had no significant reduction in their menstrual scores.

Australian researchers[14] compared the effectiveness of thermal balloon ablation (TBA) and levonorgestrel intrauterine system (LNG-IUS) in the management of idiopathic menorrhagia and changes in pictorial blood loss assessment chart (PBAC) scores in patients who had failed on oral medical treatment. They concluded that both TBA and LNG-IUS achieved significant decreases in PBAC scores, with those for the LNG-IUS being significantly greater at 12 months[14]. However, prolonged days of bleeding resulted in fewer women continuing with the LNG-IUS at two years.

The LNG IUS proved to be an effective instrument in marked reduction of blood loss compared to mefenamic acid[15]. This randomized, comparative study was based on total menstrual fluid loss (TMFL) and pictorial blood loss assessment chart (PBAC) score among fifty-one women with objective menorrhagia[15].

Both the levonorgestrel intrauterine system and oral norethisterone in a randomised comparative parallel group study at a UK teaching hospital provided an effective treatment for idiopathic menorrhagia in terms of reducing menstrual blood loss to within normal limits[16]. However, the levonorgestrel intrauterine system was associated with higher rates of satisfaction and continuation with treatment, and thus offers an effective alternative to currently available medical and surgical treatments for menorrhagia.

However, Chinese researchers suggested that thermal balloon endometrial ablation (TBEA) appeared to offer better health status function at 1 year follow-up and to be more acceptable to Chinese population compared to LNG-IUS in the treatment of idiopathic menorrhagia following failed medical treatment[17].

Both the levonorgestrel-releasing intrauterine system (LNG-IUS) and hysterectomy have proven effective for treatment of menorrhagia but the long term cost of LNG-IUS remained substantially lower than in the hysterectomy group. By providing improvement in Health-related quality of life (HRQL) at relatively low cost, the LNG-IUS may offer a wider availability of choices for the patient and may decrease costs due to interventions involving surgery[18].

A follow-up European multi-center study over 12 years of continuous use suggests that the LNG-IUS remains a safe and effective method of contraception, allowing women prolonged relief of menstrual problems and for women in their late reproductive years, offering a convenient and bleeding-free transition into the menopause[19].

A prospective, non-comparative small study of 14 DUB patients by Rokeya Begum of CMCH also reported a significant reduction of blood loss at 1 year of Mirena use[20].

The new 'frameless' FibroPlant levonorgestrel intrauterine system [21,22,23,24,25]

A novel 'frameless' intrauterine drug delivery system, the FibroPlant levonorgestrel intrauterine system (IUS), (Contrel Research, Belgium) releasing 14 microgram of levonorgestrel/day is now under study. Preliminary reports suggest that the low daily release rate of levonorgestrel from the FibroPlant levonorgestrel IUS results in a low incidence of hormonal side-effects and reduces the likelihood of amenorrhea. The simple design characteristics and revolutionary anchoring system minimize the occurrence of complaints of pain and the incidence of expulsion. The absence of a frame is particularly advantageous in women with primary and secondary dysmenorrhoea. The flexible fibrous delivery system adapts to cavities of every size even when severely distorted. These factors, together with the low incidence of amenorrhea, appear to be a significant step forward from the 'framed' levonorgestrel intrauterine system (Mirena).

Conclusion

The levonorgestrel-releasing intrauterine system Mirena is now increasingly used worldwide to control menorrhagia. The device has been a success story in this aspect saving many women from hysterectomies. It has also provided therapeutic benefits in dysmenorrhoea, premenstrual symptoms, fibroids, adenomyosis, endometriosis and even in hormone replacement therapy. LNG-IUS Mirena is still not available and used in Bangladesh. May be its time for us to start prescribing Mirena for greater benefits to our patients.

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