



Levonorgestrel-Releasing Intrauterine System Use in Perimenopausal Women

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The levonorgestrel-releasing intrauterine system (LNG-IUS) is a highly effective contraceptive method that has several noncontraceptive benefits. It has been used in various gynecological conditions, such as heavy menstrual bleeding, dysmenorrhea, and endometrial hyperplasia. During the perimenopausal period, hormonal fluctuations occur, and there is a high tendency for the development of several benign gynecologic diseases. Therefore, the use of LNG-IUS in perimenopausal women might be more beneficial than in women belonging to other age groups. Moreover, the insertion of LNG-IUS during the perimenopausal period could confer endometrial protection during estrogen replacement therapy. In this review, we discuss the use of LNG-IUS in perimenopausal women.

Key Words: Endometrial protection, Heavy menstrual bleeding, Levonorgestrel-intrauterine system, Perimenopause

INTRODUCTION

The levonorgestrel-releasing intrauterine system (LNG-IUS) was first launched in Finland in 1990 [1]. Mirena, the first marketed LNG-IUS, contains 52 mg of levonorgestrel, which is released into the uterine cavity at a rate of 20 µg/day for five years. After launching LNG-IUS 52 mg (Mirena), other types of LNG-IUSs, Kyleena and Jaydess, were also introduced into the commercial market. Kyleena contains 19.5 mg of levonorgestrel, and Jaydess—also introduced as Skyla in the USA—contains 13.5 mg of levonorgestrel.

All of these LNG-IUSs exert a contraceptive effect by thinning the endometrium and thickening the cervical mucosa. The foreign body reaction elicited by the device itself may also contribute to the contraceptive effect [2].

Despite its approved contraceptive effects by numerous studies, reluctance or discomfort per se regarding

the use of an intrauterine device (IUD) might affect its acceptance by many women that differs according to their age. Some misconceptions regarding IUD, such as possibilities of inducing infertility or pelvic inflammatory disease, and the relatively high incidence of device expulsion have been reported in adolescents and nulliparous women [3].

However, the safety of IUDs in adolescents and nulliparous women is supported by recent recommendations, as well as in perimenopausal women [4,5]. Perimenopause encompasses the period of time during which physiologic changes mark progression toward a woman's final menstrual period [6]. These changes induce varying clinical symptoms such as vasomotor symptoms, irregular bleeding and mood changes.

The use of LNG-IUSs in perimenopausal women has a different purpose than in adolescence. In perimenopausal women, the incidence of various gynecologic diseases increases, and treatment options should be

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chosen considering the timing of menopause. Most benign gynecologic diseases tend to be asymptomatic after menopause. Therefore, temporary treatment options based on the patient's symptoms, instead of surgical and definitive treatment modalities, could be adopted as first-line management in perimenopausal women.

Unlike LNG-IUS 19.5 mg (Kyleena) and LNG-IUS 13.5 mg (Jaydess), LNG-IUS 52 mg (Mirena) has proven non-contraceptive benefits in other conditions, such as the reduction of dysmenorrhea, the treatment of heavy menstrual bleeding (HMB), and the treatment and prevention of endometrial hyperplasia [1,6].

In this article, we reviewed the clinical application of LNG-IUS 52 mg in perimenopausal women (Fig. 1).

PHYSIOLOGIC CHANGES IN PERIMENOPAUSE

Perimenopausal period is induced from the decline in ovarian function. Decreased ovarian function is indicated by changes of serum hormonal level such

as a decrease in inhibin B, an increase in FSH (follicle stimulating hormone), and in decrease in AMH (anti-Mullerian hormone) [7]. Because of these hormonal changes, menstrual intervals begin to vary by 7 days or more in consecutive cycles. In the late phase of perimenopause, menstrual intervals become longer more than 60 days.

In spite of decreasing ovarian function, some hormonal dependent diseases show increasing incidence during perimenopausal period. This may be related with increased risks of anthropometric factors such as age, body weight and lifestyle changes, but atypical physiologic changes, such as luteal out of phase (LOOP), might have exerted some effects. LOOP events are defined the atypical estradiol secretion pattern appeared to originate specifically during the luteal phase of an existing ovulatory cycle [8]. This pattern has been reported 30% of cycles in women of menopausal transition with menstrual cycle irregularity. It may be explained by the out-of-phase selection of a dominant follicle during an existing luteal phase.

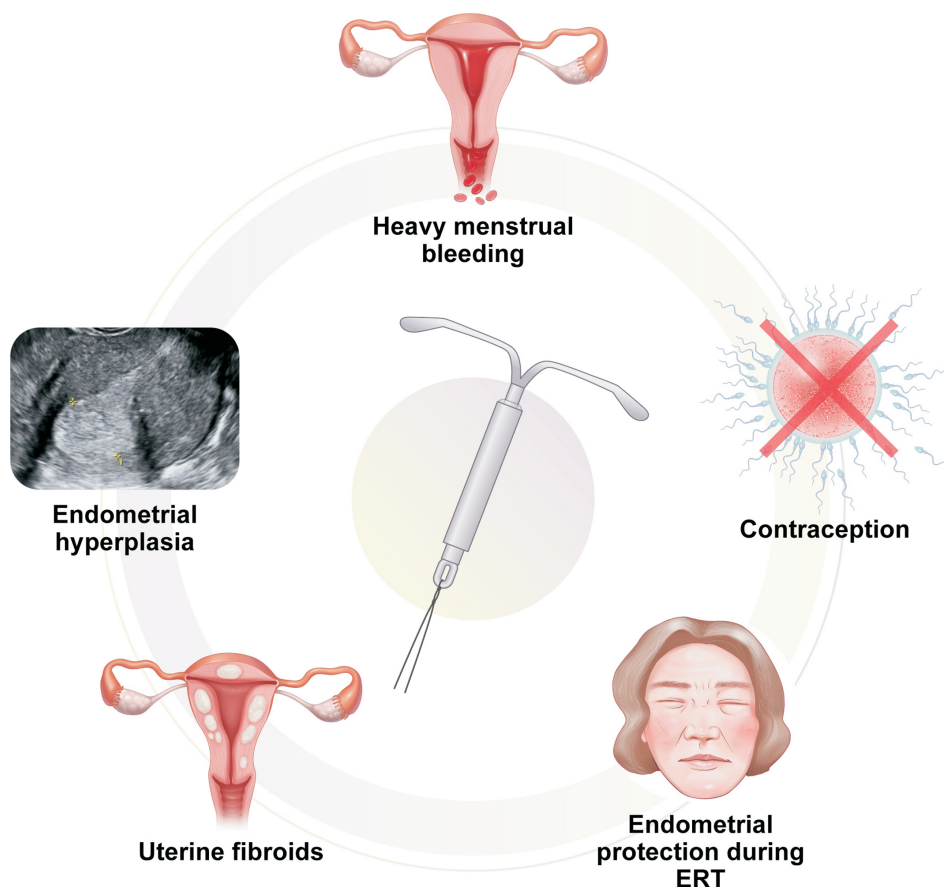


Fig. 1. Overview of levonorgestrel-releasing intrauterine system use in perimenopausal women. ERT: estrogen replacement therapy.

HEAVY MENSTRUAL BLEEDING

HMB is one of the most common gynecological symptoms in women of reproductive age and causes a deterioration in the quality of life, inconvenience in daily life and even a huge economic burden [9].

In 2011, the Federation of Gynecology and Obstetrics (FIGO) released a new classification system for abnormal bleeding, which included HMB [10]. The FIGO classification uses the PALM-COEIN system to describe the causes of HMB as polyp, adenomyosis, leiomyoma, malignancy, hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not-yet-classified. The PALM part of the system pertains to structural causes and the COEIN part is related to non-structural causes [10]. Each categorized causes, along with the age of the patient and her desire for pregnancy, significantly affect and differentiate the management of HMB according to the regarding factors.

Among various treatment modalities, the LNG-IUS is one of the most effective non-surgical treatments and is considered as the first-line treatment if no contraindications exist. Such possible contraindications include postpartum sepsis, immediate post-septic abortion, unexplained vaginal bleeding, current breast cancer, current pelvic inflammatory disease and distorted uterine cavity that is incompatible with IUD insertion [11].

Numerous randomized controlled trials and systematic reviews have supported the efficiency of the LNG-IUS in HMB. The mean reduction in pictorial blood loss assessment chart (PBAC) scores was more than 70% during the first three months of LNG-IUS insertion in the systematic review by Bitzer et al. [12]. When leiomyoma or adenomyosis is present, the LNG-IUS is also an effective method for managing HMB [13-15].

Roughly stated, the causes of HMB in perimenopausal women might not be different from premenopausal women. However, physiologic changes, such as the lengthened follicular/proliferative phase or LOOP events, could induce much heavier bleeding in perimenopausal women than premenopausal women [8]. LNG-IUS inhibits the endometrial growth and changes the prostaglandins ratio by stimulating arachidonic acid formation in the endometrium. Through these actions, it contributes to decreasing HMB in perimenopausal women.

Yoo et al. [16] further reported the efficacy of the LNG-IUS in perimenopausal women with menorrhagia. In that study, 192 women over 40 years old were

followed for two years. The amount and duration of bleeding and pain scores were recorded at 3, 6, 12, and 24 months. The continuation rate of using the LNG-IUS for 24 months was 80.78%, and the mean PBAC scores were 172.30 at pre-insertion and 7.51 at 24 months after insertion. Twenty-six patients (13.5%) failed LNG-IUS treatment and received a hysterectomy. The pain score at the third month and the amount of bleeding at the sixth month were factors affecting for undergoing a hysterectomy. In this study, 52.6% of the patients had adenomyosis, and leiomyoma was present in 17.7% of the patients. Desai [17] also reported the efficacy of the LNG-IUS in perimenopausal women. Forty women with menorrhagia were included in the study. Seventy-five percent of the patients had ovulatory/endometrial dysfunction, 12.5% had fibroids, and 10% had adenomyosis. The number of patients who complained HMB was 8 patients (20%) at 3 months and 3 patients (7.5%) at 6 months after LNG-IUS insertion. He suggested that the LNG-IUS was a safe and effective option for perimenopausal women with menorrhagia due to benign lesions of the uterus.

In another study, continuous oral or intramuscular medroxyprogesterone acetate (MPA) was compared with the LNG-IUS in perimenopausal women with menorrhagia [18]. The mean duration of menstruation was not different among the groups. However, the prevalence of side effects was different between the groups. Irregular bleeding was reported 20.4% in intramuscular MPA group, 27.2% in oral MPA group and 13.6% in LNG-IUS group. Also, the patient's will to continue the given treatment was higher in LNG-IUS group (86.3%) than intramuscular MPA (56.8%) and oral MPA group (43.1%). They suggested that the efficacy of the LNG-IUS was superior to oral and intramuscular MPA.

The supportive data are still limited, but the data reported so far indicate that the LNG-IUS is an effective and safe treatment option for HMB in perimenopausal women.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia represents a spectrum of irregular morphological alterations where the abnormal proliferation of the endometrial glands results in an increase in the gland-to-stromal ratio compared to the endometrium in the proliferative phase of the cycle [19]. Several histological classification methods that have been proposed to this point aim at correlating the

endometrial hyperplasia architecture and cytological features with the risk of progression to endometrioid endometrial cancer [20]. Endometrial hyperplasia was classified into two categories: hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN) [21].

Recently updated guidelines have recommended that the LNG-IUS should be used as the first-line treatment for endometrial hyperplasia without atypia [22,23]. Also, in the case of women with atypical hyperplasia who wish to preserve fertility, the LNG-IUS is specifically recommended as the first-line treatment [23].

Regarding perimenopausal women, Abu Hashim et al. [24] reported a significantly higher regression rate in the LNG-IUS group ($n = 59$) than in the norethisterone acetate group ($n = 61$) in perimenopausal women with endometrial non-atypical hyperplasia. In their 12-month follow-up data, the regression rate was 88.1% in the LNG-IUS group and 55.7% in the norethisterone acetate group at 12 months. Haimovich et al. [25] also reported the efficacy of the LNG-IUS in perimenopausal women with non-atypical endometrial hyperplasia. In this study, 15 women with histologically confirmed endometrial hyperplasia without atypia were included, and the mean age of patients was 49. The results of endometrial biopsy after 12 months of LNG-IUS insertion were 14 cases of atrophic endometrium (93.3%) and 1 case of secretory endometrium (6.7%). At 24 months, endometrial atrophy was documented in 100% of women.

However, there has been no report on the use of the LNG-IUS in perimenopausal women with atypical endometrial hyperplasia. In fact, the incidence of endometrial cancer increases with age, and endometrial hyperplasia is well known precancerous lesion. Therefore, treatment for endometrial hyperplasia is more important in perimenopausal women. In the endometrial hyperplasia without atypia, the progression rate to cancer was reported 2.6% per year [26]. Therefore, the use of LNG-IUS, which is recognized as the most effective drug treatment, has numerous aspects to be considered as the first-line treatment. In case of endometrial hyperplasia with atypia, the progression rate is much higher—8.2% per year. In this case, hysterectomy is the standard treatment, and there is no data on the effect of LNG-IUS in endometrial hyperplasia with atypia in perimenopausal women. However, when considering the effect in women of reproductive age, it might be considered to have similar effectiveness in perimenopausal

women, and if fertility preservation is desired, it may be considered in case of early endometrial cancer, in which the patient who have already undergone oocyte freezing or are considering oocyte donation from young women.

UTERINE FIBROIDS

Regarding the classification of leiomyoma uteri with various locations in the uterus, most studies have excluded submucosal myoma when evaluating the efficacy of LNG-IUS on leiomyoma because most submucosal myoma causes distorted endometrial cavity, which is one of the contraindications in using LNG-IUS. One could convincingly presume that the effect of device could be decreased in case of submucosal myoma, but regarding studies are lacking.

In terms of fibroid development, most uterine fibroids will regress after menopause and accordingly, the symptoms caused by the fibroids will also disappear following menopause. Therefore, during the perimenopausal period, symptomatic or even expectant management could be selected by the patients and clinicians.

However, in some cases, uterine fibroids in perimenopausal women may be associated with bleeding that is difficult to control [27]. Increased hormonal fluctuations during the perimenopausal period could induce menstrual disorders [28]. Also, uterine fibroids are related to high aromatase expression and the increased production of inflammatory markers in the endometrium [29]. In such cases, more effective medical treatment comparable to that afforded by hysterectomy is required.

In women of reproductive age, the effectiveness of LNG-IUS was proved by many clinical studies [13,14,30,31]. Kriplani et al. [14] evaluated the efficacy of LNG-IUS in reducing menstrual blood loss in myoma-related menorrhagia. In this study, the menstrual blood loss in women with myoma-related menorrhagia was reduced by 92.1%, 97.4%, 97.4%, 99.5%, and 99.5% at 3, 12, 24, 36, and 48 months, respectively, after LNG-IUS insertion. Such reduction tendency was similar to that of idiopathic menorrhagia group. Soysal and Soysal [31] compared the efficacies of LNG-IUS and thermal balloon ablation in menorrhagic patients who have at least one myoma with 50% less of its volume in the endometrial cavity. The mean decrease of PBAC scores and the mean increase of serum hemoglobin levels were assessed as primary outcomes. After 12

months, those primary outcomes showed no statistical difference. The mean decrease in PBAC scores was 345 ± 42 in LNG-IUS group and 338 ± 47 in thermal balloon ablation group, and the mean increase of hemoglobin value was 2.6 ± 0.9 in LNG-IUS and 3.0 ± 1.0 in thermal balloon ablation group.

Regarding the use of LNG-IUS in perimenopausal women with uterine fibroids, only one study has been conducted. This study was conducted to determine the percentage of hysterectomies avoided by the insertion of a LNG-IUS in perimenopausal women with uterine fibroids. Hysterectomy avoidance was reported in 89.5% of 39 patients at a 24-month follow-up [27]. The authors concluded that in perimenopausal women with symptomatic uterine fibroids previously referred for surgery, the use of the LNG-IUS was associated with fewer hysterectomies and a higher degree of satisfaction. The studies that assessed the LNG-IUS use in perimenopausal women with various benign gynecologic diseases are presented in Table 1.

ENDOMETRIAL PROTECTION DURING ESTROGEN REPLACEMENT THERAPY

Before entry into menopausal transition, symptoms associated with hormonal fluctuations are reported [32]. A recent study reported that hot flushes are experienced by up to 55% of women before any evidence of menstrual irregularity [33]. Hormonal therapy is the most effective treatment for these menopausal symptoms. However, the choice for a hormonal therapy regimen should be individualized based on personal risk

factors and the quality of life [34].

All non-hysterectomized women should receive concomitant progestin with estrogen replacement therapy, and the LNG-IUS is an effective way to protect the endometrium and to manage bleeding in women using estrogen replacement therapy during the perimenopausal period [34].

Boon et al. [35] reported the efficacy on endometrial protection, vaginal bleeding patterns, blood loss and practical use in 200 perimenopausal women who had been randomly received LNG-IUS combined with oral estradiol (2 mg daily) or a cyclic oral regimen of norethisterone acetate (1 mg on day 13 to 22) and estradiol (2 mg on days 1 to 21 and 1 mg on days 22 to 28). Both regimens showed adequate endometrial protection. The cyclic regimen was better in regular bleeding pattern, and reduction in bleeding was induced more efficiently in LNG-IUS group. They suggested acceptable compliance in both groups.

Depypere et al. [36] studied the use of LNG-IUS in transition from reproductive age for contraception to menopausal age for endometrial protection during estrogen replacement therapy. Among 394 women who had inserted LNG-IUS for contraception, 168 women continuously used the LNG-IUS for endometrial protection during estrogen replacement therapy. Days of vaginal spotting and bleeding were not significantly different between the last contraceptive and first reference period of estrogen replacement phase. The observed continuation rate was 89.9% at 6 months after the initiation of estrogen replacement therapy. Pivotal studies that evaluated the endometrial protection by

Table 1. Summary of studies that assessed LNG-IUS use in perimenopausal women

Disease	Study	Study design	No. of subjects	Main results
Heavy menstrual bleeding	Yoo et al. [16]	Retrospective	192	80.7% success rate of LNG-IUS 13.5% women failed with LNG-IUS
	Desai [17]	Prospective observational	40	33 women continued to use LNG-IUS
	Küçük and Ertan [18]	RCT	44 (DMPA), 44 (MPA 5 mg daily), 44 (LNG-IUS)	LNG-IUS, superior to DMPA and MPA in PBAC scores and hemoglobin levels
Non-atypical endometrial hyperplasia	Abu Hashim et al. [24]	RCT	60 (LNG-IUS), 60 (NET)	Higher regression rate in LNG-IUS group Higher hysterectomy rate in NET group (57.4% vs. 22%)
	Haimovich et al. [25]	Open, prospective	15	Regression rate at 12 months: 100%
Uterine fibroids	Machado et al. [27]	Prospective observational	60	At 24 months, hysterectomy avoidance rate, 89.5%

LNG-IUS: levonorgestrel-intrauterine system, RCT: randomized controlled trial, DMPA: depo-medroxyprogesterone acetate, MPA: medroxyprogesterone acetate, PBAC: pictorial blood loss assessment, NET: norethisterone acetate.

the LNG-IUS during estrogen replacement therapy are summarized in Table 2 [35-40].

CONTRACEPTION

Contraception is also an important issue during the perimenopausal period. The LNG-IUS could be an effective method to achieve successful contraception without increasing any related complications in compared to that of the young-aged group.

The unintended pregnancy rate in perimenopausal women is similar to that of other age groups, which have been reported as approximately 40% [41]. Such report implies many perimenopausal women remain sexually active. Also, the risk of pregnancy-related complications could be greater in perimenopausal women than in women of early reproductive age. Consequently, counselling for contraception is an important health issue in perimenopausal women.

LNG-IUS is highly effective contraceptive method with long-acting and reversible features. The contraceptive failure rate is 0.1% per year in typical use [42]. A 52 mg and 19.5 mg LNG-IUSs are currently approved for contraception for up to 5 years and 13.5 mg LNG-IUS is approved for up to 3 years.

Although there is no specific contraindication related to age of the patient for using reversible contraception, practitioners have to consider the possibility of increasing frequency and severity of health problem caused by certain hormonal contraceptive method in old aged women [41]. In case of LNG-IUS, the contraceptive

effect is mainly achieved by local effect such as endometrial suppression and increased cervical mucus. In addition, it is widely known that hormonal contraceptives including general birth control pills increases the risk of venothromboembolism (VTE) two-to sixfold than in non-users [43]. Fortunate enough, progesterone-only contraceptives, such as LNG-IUD, have been reported to be less associated with such critical complications. This makes LNG-IUD eligible for safe use in perimenopausal women with increasing various risks of metabolic disorders.

Thus, comparing to other hormonal contraceptives, the systemic side effects might be less likely to be observed in LNG-IUS.

SIDE EFFECTS

The side effects of the LNG-IUS may not be critically different between perimenopausal women and women of reproductive age. Yet, for the sake of broad and safe application of LNG-IUS, more comprehensive studies in various age groups are needed.

Since menopausal transition can be associated with increase of body weight, the potential effect of certain contraception type on the patient's body weight could be one of important factors in choosing the suitable contraception method in perimenopausal women [44-46]. Napolitano et al. [47] reported preliminary study that evaluated the effect of 12 months' use of a desogestrel-only contraceptive pill or the LNG-IUS on body composition in perimenopausal women. In their study,

Table 2. Summary of key clinical trials using LNG-IUS for endometrial protection in perimenopausal women

Study	Population, mean age (y)	No. of subjects	Treatment duration	Endpoints
Boon et al. [35] RCT (open-label)	Perimenopausal; 46.9 (LNG-IUS), 46.8 (oral NETA)	97 (LNG-IUS), 99 (oral NETA)	2 y	Endometrial protection assessed by histology, bleeding pattern, efficacy, overall acceptability
Andersson et al. [37] RCT (open-label)	Perimenopausal; 48.1 (LNG-IUS), 48.7 (oral HRT)	18 (LNG-IUS), 19 (oral LNG 250 µg on day 11-21)	1 y	Climacteric symptoms, bleeding pattern, endometrial protection assessed by histology
Depypere et al. [36] non-randomized (open-label)	Peri/postmenopausal; 47.8	394 (contraception phase), 168 (ERT phase)	9-48 mo contraception phase, 1-5 y ERT phase	Bleeding pattern, QoL, LNG-IUS continuation, adherence, tolerability
Suhonen et al. [38] non-comparative	Peri/postmenopausal; 52	29 (LNG-IUS)	38 mo	Endometrial protection assessed by histology and transvaginal ultrasound, bleeding pattern
Suhonen et al. [39,40] non-comparative	Peri/postmenopausal; 51.4	36 (LNG-IUS)	5 y	Endometrial protection assessed by histology

LNG-IUS: levonorgestrel-intrauterine system, RCT: randomized controlled trial, NETA: norethindrone acetate, HRT: hormone replacement therapy, LNG: levonorgestrel, ERT: estrogen replacement therapy, QoL: quality of life.

both contraception methods showed significant increase of the patient's fat mass comparing to the control group. However, the LNG-IUS use showed lesser extent of such increase than desogestrel-only pill group; the increases of the patient's fat mass were $2.8\% \pm 3.5\%$ in desogestrel-only pill group, $1.1\% \pm 2.9\%$ in LNG-IUS group and -0.5 ± 1.6 in control group, respectively.

Other than the possibly increasing body weight with menopausal transition, the major concerns for using hormonal therapy in women include the potential breast cancer development; however, the results of studies regarding breast cancer and LNG-IUS are rather inclusive. Recently published meta-analysis indicated increased breast cancer risk in LNG-IUS users: for all women, odds ratio (OR) = 1.16 (95% confidence interval [CI] 1.06–1.28); for women aged younger than 50 years, OR = 1.12 (95% CI 1.02–1.22); and for women aged 50 or more years, OR = 1.52 (95% CI 1.34–1.72) [48]. On the contrary, some researchers asserted that it may not be appropriate to claim that LNG-IUS use is a risk factor for breast cancer due to the methodological concerns such as data overlap and statistical errors [49,50]. Thus, more research is needed to reach the reasonable conclusion, as studies focused on the breast cancer and LNG-IUS are much deficient.

On the other hand, when considering such association especially in women of perimenopausal years, the LNG-IUS has not been associated with an increased total risk of breast cancer as described in a recent study [51]. Yet, one must bear in mind that only a few studies have evaluated the side effects of the LNG-IUS in perimenopausal women.

CONCLUSION

We have reviewed the use of the LNG-IUS in perimenopausal women. As in other age groups, the LNG-IUS showed non-contraceptive benefits in perimenopausal women with various gynecologic diseases, such as HMB, endometrial hyperplasia, and uterine fibroid. Beside the non-contraceptive benefits, the LNG-IUS is a highly effective contraception method and can be used successfully for endometrial protection during estrogen replacement therapy. Furthermore, there has been no report regarding the incidence of its side effect especially in perimenopausal women. The use of LNG-IUS might exert similar side effects, if any, in both perimenopausal women and women of reproductive age. These features suggest that the LNG-IUS is more useful

in perimenopausal women than in other age groups.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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