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Role of Levonorgestrel Medicated Intrauterine Device in Adenomyosis

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Abstract

Adenomyosis is a benign, estrogen-dependent gynecological disorder characterized by the invasion of endometrial glands and stroma into the myometrium, leading to menorrhagia, dysmenorrhea, and infertility. Despite its prevalence, the etiology remains unclear. Conventional treatments such as hysterectomy, uterine artery embolization, and high-intensity focused ultrasound (HIFU) are effective but may not preserve fertility. Therefore, medical management is often preferred, with hormonal therapies playing a central role. The levonorgestrel-releasing intrauterine system (LNG-IUS) has emerged as a highly effective, minimally invasive treatment option. It continuously releases 20 µg/day of levonorgestrel, exerting localized effects on the endometrium and myometrium. The mechanism involves decidualization and atrophy of the endometrium, suppression of estrogen receptors, and reduction of prostaglandin production, which collectively alleviate pain and reduce menstrual bleeding. Numerous clinical studies confirm that LNG-IUS significantly decreases uterine volume, menstrual blood loss, and dysmenorrhea severity over long-term use, with a favorable safety profile compared to systemic hormonal therapies. Adverse effects are generally mild and transient, including irregular bleeding and hormonal symptoms. Overall, the LNG-IUS not only provides effective contraception but also serves as an efficient therapeutic option for adenomyosis, improving patients' quality of life and avoiding more invasive procedures. Future research should further assess its long-term outcomes and potential role in combination therapies for optimal symptom control and uterine preservation.

Key words: Adenomyosis, Levonorgestrel, Intrauterine Device, Hormonal Therapy.

Introduction:

Adenomyosis is a common estrogen-dependent, a benign gynecological disease characterized by endometrial glands and stroma invading, implanting, and proliferating in the myometrium to form diffuse or localized lesions. Its primary clinical symptoms are dysmenorrhea, menorrhagia, and infertility in women of reproductive age **(1)**. Nevertheless, the etiology and pathogenesis of this disorder remain unclear.

Depending on disease development and patients' desire to conceive, many conservative surgical choices, including lesion resection, endometrial ablation, uterine artery embolization (UAE), and high-intensity focused ultrasound (HIFU), are offered to relieve severe symptoms. However, women with adenomyosis, who have residual lesions, generally require long-term medical management after conservation surgery, and medication is the mainstream treatment. Gonadotropin-releasing hormone agonist (GnRHa) cannot be used for long periods due to its high price and multiple side-effects, including reduced estrogen levels **(2)**.

The levonorgestrel-releasing intrauterine device (LNG-IUD) is widely used for its therapeutic effects, including the release of synthetic progesterone at a rate of 20 ug/day. Many published reports have verified its long-term effects in the treatment of uterine adenomyosis over 3 years **(3)**.

Adenomyosis

Adenomyosis may be defined as the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium **(4)**

- **Epidemiology**

Accurate demographics and disease prevalence are unclear due to previous underreporting and under-diagnosis. Estimates range from 5% to 70% with more recent data suggesting a prevalence of 20% to 35%. Classically, adenomyosis is described as a disease of pre-menopausal, multiparous women in their thirties to forties; however, this reflects the inherent bias towards women undergoing a hysterectomy **(5)**.

A rare form of the disease, termed juvenile cystic adenomyosis, is characterized by more extensive hemorrhage within myometrial cysts and is typically seen in women younger than 30 **(6)**.

- **Etiology**

While the histology is well-described, the etiology of adenomyosis is not known definitively. Researchers have postulated several theories. The most commonly accepted theory is that adenomyosis results from a disrupted boundary between the deepest layer of the endometrium (endometrium basalis) and the underlying myometrium. This process leads to a cycle of inappropriate endometrial proliferation into the myometrium with subsequent small vessel angiogenesis as well as adjacent myometrial smooth muscle hypertrophy and hyperplasia. Data demonstrating a higher prevalence of adenomyosis following dilation and curettage and cesarean section support this theory **(7)**.

A second theory proposes an embryologic mechanism whereby pluripotent Mullerian stem cells undergo inappropriate differentiation leading to ectopic endometrial tissue. This theory has support from evidence demonstrating altered expression of specific genetic markers, in addition to case reports of endometrial tissue found in women with Rokitansky-Kuster-Hauser syndrome (Mullerian agenesis) **(8)**.

Other less well-accepted theories propose altered lymphatic drainage pathways and displaced bone marrow stem cells to explain the presence of ectopic endometrial tissue **(9)**.

- **Risk Factors**

- **Age:** 70 to 80% of women undergoing hysterectomy for adenomyosis are in their fourth and fifth decade of life and are multiparous; several studies have reported a mean age over 50 years for women undergoing hysterectomy for adenomyosis **(10)**.
- **Multiparity:** A high percentage of women with adenomyosis are multiparous **(11)**.
- **Prior uterine surgery:** Evidence regarding a significantly increased risk of prior uterine surgery in women with adenomyosis is inconsistent **(7)**
- **Smoking:** Evidence regarding an association between smoking and adenomyosis is controversial. On the one hand, in comparison with women who never smoked, smokers appear less likely to have adenomyosis. This finding can be explained by hormonally induced mechanisms: decreased serum levels of estrogen have been reported in smokers, and adenomyosis has been suggested to be an estrogen-dependent disorder **(12).**
- **Depression and antidepressant use:** Novel associations with adenomyosis found in both human and animal studies include an increased risk of depression, and higher antidepressant use **(13)**
- **Tamoxifen treatment:** Adenomyosis is relatively rare in postmenopausal women but a higher incidence of adenomyosis has been reported in women treated with tamoxifen for breast cancer **(14)**.

- **Pathophysiology**

Inappropriate endometrial tissue proliferation within the myometrium leads to symptoms through a variety of mechanisms. Normal endometrial tissue is responsible for prostaglandin production which drives the contractions of menstruation. Ectopic foci of adenomyosis lead to increased levels of prostaglandins which result in dysmenorrhea

which characterizes the disease. Estrogen also drives endometrial proliferation, which medical therapies aim to reduce **(6)**.

Heavy menstrual bleeding is thought to be caused by a combination of factors which include increased endometrial surface area, increased vascularization, abnormal uterine contractions, and increased cell signaling molecules such as prostaglandins, eicosanoids, and estrogen **(9)**.

➢ **Diagnosis of adenomyosis**

✓ **Laboratory Evaluation**

Laboratory testing is useful to rule out other disease entities included in the differential diagnosis, in addition to identifying certain complicating features such as anemia due to heavy menstruation. While some biomarkers do exist, none are specific for adenomyosis **(5)**

✓ **Imaging**

o **Ultrasound:** Transvaginal ultrasound (TVS) represents a cost-effective initial screening modality for adenomyosis. Ultrasound features of adenomyosis can be divided into direct or indirect features. Direct features are due to the presence of endometrial tissue within the myometrium, and indirect features are due to a hypertrophied myometrium **(15)**.

o **Magnetic resonance imaging (MRI):** MRI represents a second line, detailed imaging modality for the detection of adenomyosis. Similar to ultrasound, various direct and indirect features can be used to describe adenomyosis, but need more knowledge of uterine anatomy and its cyclic variations **(16)**.

➢ **Treatment**

The first consideration in treatment selection is the desire for fertility, which will guide treatment considerations. Hysterectomy is the definitive cure. The remaining options target the primary symptoms of heavy, painful menstrual bleeding while preserving the uterus **(6)**.

✓ **Medical treatment**

Medical treatment is the first-line treatment option for adenomyosis aiming to relieve symptoms and maintain fertility with the least possible side effect. This is achieved by disrupting pathways leading to inflammation, neuroangiogenesis, and impaired apoptosis **(17)**.

▪ **Nonsteroidal anti-inflammatory drugs (NSAIDs)** are one of the primary medical therapies. These medications target the cyclooxygenase enzyme which produces the prostaglandins responsible for painful cramping during menstruation **(9)**.

▪ **Various hormonal therapies** are available which include oral contraceptive pills (OCPs), danazol and aromatase inhibitors. These therapies aim to reduce the estrogenic effects which lead to endometrial proliferation **(6)**.

▪ **Levonorgestrel Intrauterine Device (IUD)** are generally considered to be the primary therapy due to decreased side effect profile and overall success rates **(9)**.

✓ **Minimally Invasive/Surgical Therapies**

These are second-line treatment options aiming to cure symptoms and preserve the uterus in patients with failed medical therapy. Conservative surgical treatments aim to remove adenomyosis and preserve the remaining normal uterine muscles through laparotomy, laparoscopy, hysteroscopy, or combined approach. Excisional adenomyomectomy involves the complete removal of focal lesions (adenomyomas), while myometrectomy is the surgical debulking of diffuse adenomyosis. Non-excisional treatments aim to induce necrosis of focal or diffuse adenomyosis through selective vascular occlusion or focused ultrasound/thermal energy without direct tissue dissection. In some cases, a combination of surgical and non-excisional methods, i.e., hysteroscopic resection/ablation, are used to achieve maximum cytoreduction and reduce myometrial tissue damage **(15)**.

✓ **Conservative Surgical Treatment**

Debulking/cytoreductive surgeries aim to remove visibly diseased tissue with repair of the remaining myometrial tissue. The main issue with conservative surgical methods is the high risk for complications, i.e., uterine rupture and complicated pregnancy (especially in diffuse lesions and on long-term follow-up), making this option safer in focal adenomyomas **(18)**.

✓ **Hysteroscopic resection/ablation**

Hysteroscopic resection/ablation is a combined treatment method involving the dissection and or coagulation of cystic adenomyotic lesions and crypts **(19)**.

✓ **High-intensity focused ultrasound (HIFU)**

High-intensity focused ultrasound (HIFU) is the use of intense ultrasound energy directly targeting abnormal tissues and their vascularity through heating and cavitation, sparing the normal surrounding tissues. This process can be guided and monitored through MRI or ultrasound. High-intensity focused ultrasound has been used since 2008 for the treatment of adenomyosis **(20)**.

✓ **Uterine artery embolization (UAE)**

Uterine artery embolization is the use of transarterial catheters aiming to induce more than 34% necrosis within adenomyotic tissues **(21)**. The technique for UAE in adenomyosis is similar to that used in fibroids. In many parts of the world, UAE is performed under conscious sedation.

➢ **Complications**

The correlation between adenomyosis and infertility is not clearly defined. While some authors cite an association of 11% to 12%, contradictory data also exists. Due to a multitude of confounders and variable diagnostic criteria for adenomyosis, no clear association has been established **(5)**.

With more validated diagnostic imaging criteria of ultrasound in recent years, future research will be able to characterize associations between adenomyosis and infertility more confidently **(6)**.

The levonorgestrel-releasing intrauterine system (LNG-IUS)

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a safe, effective and acceptable form of contraception used by over 150 million women worldwide. It also has a variety of noncontraceptive benefits including treatment for menorrhagia, endometriosis, and endometrial hyperplasia. The LNG-IUS has also been used in combination with estrogen for hormone replacement therapy and as an alternative to hysterectomy. Overall, the system is very well tolerated and patient satisfaction is quite high when proper education regarding possible side effects is provided **(22)**.

✓ **Indications**

Based on the fact that there are two different types of IUDs, including levonorgestrel and copper-containing, it should be understood that there are different indications for each of these. All IUDs are indicated for the use of contraception. For the levonorgestrel-containing IUD, there are three different strengths of levonorgestrel available, 13.5 mg, 19.5 mg, and 52 mg. They are all equally effective at providing reliable contraception. However, the higher dose IUD, 52 mg device, is also approved for the treatment of menorrhagia and endometrium protection during hormone replacement therapy **(23)**

✓ **Insertion Procedure Proper**

LNG IUS insertion is important for proper positioning within the uterus, lessening the risk of infection, perforation and expulsion, as well as ensuring uniform dispersion of LNG over the endometrium. The LNG IUS should be inserted within 7 days from the onset of menstruation (because the low likelihood of pregnancy during this time)**(24)**.

- 6 weeks or longer (until full involution of the uterus) after childbirth
- Immediately after menstrual regulation or first trimester spontaneous or induced abortion, provided there is no infection

Acceptors of LNG IUS must be screened and cleared of STIs, and it is the providers' responsibility to inspect the woman's reproductive tract, both externally and internally, for signs and symptoms of infection. LNG IUS acceptors should be counseled before device insertion, and provided with an opportunity to ask questions and refuse insertion, if desired **(22)**.

✓ **Mechanism of action of the LNG-IUS**

The LNG-IUS provides highly effective contraception for up to five years, with potential for approval for up to seven years in the near future. The mechanisms of action of the LNG-IUS are similar to that of levonorgestrel implants or levonorgestrel-containing mini-pills, although it accomplishes these effects with much lower peak serum levels than other progestin-containing contraceptives (0.1–0.4 ng/ml vs 1.7–15.2 ng/ml with combined and progestin-only oral contraceptives, respectively, and 5.4 ng/ml for combined vaginal preparations)**(22)**

The LNG-IUS is a T-shaped device composed of a cylinder containing 52 mg of LNG covered by a rate-controlling membrane which serves to regulate the rate of hormonal release. Initially, 20 μg of levonorgestrel is released every 24 hours from this polymer cylinder. This decreases to 11 μg every 24 hours by the end of five years, with an average release rate of 14 μg per day over the life of the IUS. Levonorgestrel, a highly potent second generation progestin, thickens cervical mucus and suppresses endometrial proliferation (preventing decidualization of the stroma). This creates a hostile environment for sperm survival, inhibiting motility and capacitation with the net effect combining to prevent fertilization **(25)**.

✓ **LNG IUS Method Acceptors**

LNG IUS may be appropriate for all women of reproductive age who need contraception, including women who breastfeed; there are no age or parity restrictions on its use. Today, LNG IUS use among women who have not yet demonstrated their fertility, and use among women with multiple partners, is not contraindicated, yet use of other contraceptive methods should be encouraged. Other contraindications include pregnancy, pelvic inflammatory disease, gynecologic infections, cervical or uterine abnormalities and cancers, among others. Thepatient must be properly assessed and properly counseled about these contraindications before LNG IUS insertion **(26)**.

✓ **Efficacy of the levonorgestrel-releasing IUS: (27)**

- The IUD, in general, is one of the most effective forms of contraception available today, with a global cumulative pregnancy rate of <2% at five years. The LNG-IUS, in particular, is possibly the most effective IUD available according to numerous studies that show its global cumulative pregnancy rate to be <0.5%.22
- The LNG-IUS is also an effective option for women to choose immediately post abortion. A LNG-IUS may, therefore, be safely inserted immediately after either uncomplicated spontaneous or induced abortions.
- The levonorgestrel-releasing intrauterine system can also be safely inserted immediately after childbirth, but there is also an increased risk of expulsion compared with interval insertion.

✓ **Side Effects**

Most side effects associated with LNG-IUS use are not serious. Changes in menstrual bleeding patterns are the most common side effect. Additionally, women using LNG IUS occasionally develop enlarged ovarian follicles that rarely cause any symptoms. Ectopic pregnancies have occurred in LNG IUS users, yet the device is actually protective

against ectopic pregnancies. Pelvic Inflammatory Disease (PID) is a potential serious complication with LNG IUS use and often requires device removal and antimicrobial medication, yet risk of PID may be smaller than with copper IUDs. In rare instances (less than 1 per 1000 insertions), uterine perforation takes place, which is mainly associated with improper insertion of device. Other conditions that may or may not be associated with LNG IUS use include headaches, edema, breast tenderness, weight gain, vaginal discharge, cervicitis, dysmenorrhea, nervousness, depressive mood, mental lability, pelvic pain, nausea and acne **(28)**.

Noncontraceptive benefits of LNG-IUS

- **The LNG-IUS as treatment for menorrhagia**

Menorrhagia, defined as >80 mL of menstrual blood loss. There are a variety of medical and surgical treatments available for menorrhagia, including prostaglandin synthetase inhibitors, antifibrinolytic agents, oral contraceptive pills, and endometrial ablation. However, most of these treatments have only been shown to improve menstrual bleeding by 20%–50%. In addition, the associated side effects and repetitive nature of these treatments significantly impairs patient compliance. In contrast, the LNG-IUS has been used in numerous studies as a treatment of menorrhagia, with a reduction in menstrual blood flow of 86%–97% **(29)**.

- **The LNG-IUS as treatment for endometriosis**

Endometriosis is associated with chronic pelvic pain, dyspareunia and infertility, and is often a significant detriment to a patient's quality of life. Treatment has historically consisted of some combination of nonsteroidal anti-inflammatory medications (NSAIDs), progestational medications such as depot medroxyprogesterone acetate (DMPA) that function as anti-estrogens, ovulation suppression with oral contraceptive pills, androgenic medications such as danazol, gonadotropin-releasing hormone (GnRH) analogues to induce temporary pseudo-menopause, and surgical ablation. The LNG-IUS has recently been studied as an alternative for treating the pain and symptoms associated with endometriosis, as it addresses both the patient compliance and the long-term use issues **(22)**.

- **The LNG-IUS as treatment for endometrial hyperplasia**

Endometrial hyperplasia is classified according to increasingly abnormal architectural and cytologic criteria as simple, complex, and atypical hyperplasia. Cytologic atypia is the most important prognostic factor with regard to progression to endometrial cancer. Hysterectomy is generally considered to be the standard of care unless the patient desires to retain potential fertility or there are medical contraindications to surgery. In contrast, because nonatypical hyperplasia is generally considered to be low risk for progression to cancer, many patients and providers consider hysterectomy too invasive a treatment. Though there is no consensus on the best way to treat these women, they have often been treated with oral progestins **(22)**.

However, because of the systemic nature of the treatment there can be significant side effects that limit compliance with treatment, and when the treatment is discontinued the hyperplasia can recur. As a result, numerous studies have been done to evaluate the LNG-IUS as an alternative therapy to hysterectomy for those with endometrial hyperplasia without atypia. This expression declined significantly, marking the strong antiproliferative effect of the LNG-IUS, with its inhibition of estrogen bioactivity and suppression of the endometrium **(30)**. The studies indicate that the LNG-IUS is a superior treatment modality for endometrial hyperplasia than low dose oral progestins or observation alone.

- **The LNG-IUS as treatment for adenomyosis**

Adenomyosis is a relatively common disorder affecting women, usually in their 40s and 50s, characterized by the presence of heterotopic endometrial glands and stroma in the myometrium with hyperplasia of the adjacent smooth muscle. The symptoms include menorrhagia (40%–50%), dysmenorrhea (15%–30%), and metrorrhagia (10%–12%). The options for this condition include endometrial ablation, danazol and GnRH agonists. However, endometrial ablation is not effective for this condition as it does not penetrate deeply enough into the myometrium **(22)**.

In addition, as discussed previously with regards to treatment for endometriosis, in light of the side effects of the other forms of medical treatment listed, the LNG-IUS is becoming an increasingly attractive option for treatment of

adenomyosis. It is hypothesized to work on adenomyosis in two ways. First, as discussed earlier, it causes decidualization and atrophy of the endometrium, therefore decreasing the amount of menstrual flow. Secondly, the levonorgestrel down regulates estrogen receptors in glandular and stromal endometrial tissues. This likely prevents further estrogen stimulation of the adenomyosis foci within the myometrium, causing them to atrophy and shrink. This may lead to decreased menstrual flow by allowing the myometrium to better contract, limiting the blood loss during menses, and also accounts for the decreased size of the uterus noted **(22)**.

Conclusion

The levonorgestrel-releasing intrauterine device (LNG-IUS) represents a safe, effective, and fertility-preserving treatment for adenomyosis. By delivering continuous local hormonal therapy, it successfully reduces menstrual bleeding, pelvic pain, and uterine size, with minimal systemic side effects. Compared to other medical or surgical options, LNG-IUS provides long-term symptom relief and high patient satisfaction. Thus, it should be considered a first-line therapy for women seeking non-surgical management of adenomyosis, especially those desiring to retain fertility.

References:

1. **Exacoustos C, Zupi E**. A new era in diagnosing adenomyosis is coming. Fertil Steril. 2018;110(5):858.
2. **Vannuccini S, Luisi S, Tosti C, Sorbi F, Petraglia F**. Role of medical therapy in the management of uterine adenomyosis. Fertil Steril. 2018;109(3):398–405.
3. **Chen S, Wang J, Sun W, Zhu L, He J, Zhang X**. Efficacy of the levonorgestrel-releasing intrauterine device is associated with different subtypes of adenomyosis: a retrospective study. Ann Transl Med. 2020;8(21):1356.
4. **Guy MM, Ying WZ, Yan WX, Hui FZ, Hai WX, Ping LY, et al.** Effectiveness of treatment for infertility using clinical investigation of laparoscopy cytoreductive surgery combined with gestrinone in adenomyosis. Gynecol Surg. 2016;13(4):451–6.
5. **Abbott JA**. Adenomyosis and abnormal uterine bleeding (AUB-A)—pathogenesis, diagnosis, and management. Best Pract Res Clin Obstet Gynaecol. 2017;40:68–81.
6. **Gunther R, Walker C**. Adenomyosis. In: StatPearls [Internet]. StatPearls Publishing; 2023.
7. **Taran FA, Stewart EA, Brucker S**. Adenomyosis: epidemiology, risk factors, clinical phenotype and surgical and interventional alternatives to hysterectomy. Geburtshilfe Frauenheilkd. 2013;73(09):924–31.
8. **Mehasseb MK, Panchal R, Taylor AH, Brown L, Bell SC, Habiba M**. Estrogen and progesterone receptor isoform distribution through the menstrual cycle in uteri with and without adenomyosis. Fertil Steril. 2011;95(7):2228–35.
9. **Struble J, Reid S, Bedaiwy MA**. Adenomyosis: a clinical review of a challenging gynecologic condition. J Minim Invasive Gynecol. 2016;23(2):164–85.
10. **Lonky NM, Chiu V, Portugal C, Estrada EL, Chang J, Fischer H, et al.** Adenomyosis in women undergoing hysterectomy for abnormal uterine bleeding associated with uterine leiomyomas. PLoS One. 2023;18(12):e0294925.
11. **Bieber EJ, Sanfilippo JS, Horowitz IR, Shafi MI**. Clinical gynecology. Cambridge University Press; 2015.
12. **García-Solares J, Donnez J, Donnez O, Dolmans MM**. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertil Steril. 2018;109(3):371–9.
13. **Rossi M, Vannuccini S, Capezzuoli T, Fambrini M, Vannuzzi V, Donati C, et al.** Mechanisms and pathogenesis of adenomyosis. Curr Obstet Gynecol Rep. 2022;11(2):95–102.

14. **Tetikkurt S, Çelik E, Taş H, Cay T, Isık S, Usta AT**. Coexistence of adenomyosis, adenocarcinoma, endometrial and myometrial lesions in resected uterine specimens. Mol Clin Oncol. 2018;9(2):231–7.

15. **Dessouky R, Gamil SA, Nada MG, Mousa R, Libda Y**. Management of uterine adenomyosis: current trends and uterine artery embolization as a potential alternative to hysterectomy. Insights Imaging. 2019;10(1):48.

16. **Bazot M, Daraï E**. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril. 2018;109(3):389–97.

17. **Vannuccini S, Tosti C, Carmona F, Huang SJ, Chapron C, Guo SW, et al.** Pathogenesis of adenomyosis: an update on molecular mechanisms. Reprod Biomed Online. 2017;35(5):592–601.

18. **Osada H**. Uterine adenomyosis and adenomyoma: the surgical approach. Fertil Steril. 2018;109(3):406–17.

19. **Sun W, Guo X, Zhu L, Fei X, Zhang Z, Li D**. Hysteroscopic treatment of a uterine cystic adenomyosis. J Minim Invasive Gynecol. 2018;25(3):374–5.

20. **Cheung VYT**. Current status of high-intensity focused ultrasound for the management of uterine adenomyosis. Ultrasonography. 2017;36(2):95–102.

21. **Dueholm M**. Minimally invasive treatment of adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2018;51:119–37.

22. **Beatty MN, Blumenthal PD**. The levonorgestrel-releasing intrauterine system: Safety, efficacy, and patient acceptability. Ther Clin Risk Manag. 2009;561–74.

23. **Grandi G, Farulla A, Sileo FG, Facchinetti F**. Levonorgestrel-releasing intra-uterine systems as female contraceptives. Expert Opin Pharmacother. 2018;19(7):677–86.

24. **Zhang GR, Yu X**. Perforation of levonorgestrel-releasing intrauterine system found at one month after insertion: A case report. World J Clin Cases. 2023;11(1):172.

25. **Miglani U, Singh P**. Levonorgestrel intrauterine releasing system: long term health impact. Int J Reprod Contracep Obs Gynecol. 2015;4:795–800.

26. **Zgliczynska M, Kocaj K, Szymusik I, Dutsch-Wicherek MM, Ciebiera M, Kosinska-Kaczynska K**. Levonorgestrel-releasing intrauterine system as a contraceptive method in nulliparous women: a systematic review. J Clin Med. 2020;9(7):2101.

27. **Fanse S, Bao Q, Burgess DJ**. Long-acting intrauterine systems: recent advances, current challenges, and future opportunities. Adv Drug Deliv Rev. 2022;191:114581.

28. **Kim ML, Seong SJ**. Clinical applications of levonorgestrel-releasing intrauterine system to gynecologic diseases. Obstet Gynecol Sci. 2013;56(2):67–75.

29. **Marjoribanks J, Lethaby A, Farquhar C**. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database Syst Rev. 2016;(1).

30. **Wildemeersch D, Janssens D, Pylyser K, De Wever N, Verbeeck G, Dhont M, et al.** Management of patients with non-atypical and atypical endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: long-term follow-up. Maturitas. 2007;57(2):210–3.