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Safety And Efficacy of The Levonorgestrel-Releasing Intrauterine System in Treatment of Endometrial Hyperplasia: Review Article

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ABSTRACT

Background: Endometrial hyperplasia (EH) is a proliferative disorder of the endometrial lining, primarily resulting from prolonged unopposed estrogen exposure. It is a recognized precursor to endometrial carcinoma, particularly among perimenopausal women. The levonorgestrel-releasing intrauterine system (LNG-IUS) has proven to be an efficient, localized hormonal management for endometrial hyperplasia, particularly for non-atypical types.

Objective: This review article aimed to throw the light on the safety and efficacy of the levonorgestrel-releasing intrauterine system in treatment of endometrial hyperplasia.

Methods: We used Google Scholar, Science Direct, PubMed, and other internet databases for Endometrial hyperplasia, Non-atypical hyperplasia, Levonorgestrel-releasing intrauterine system, Hormonal therapy. Additionally, the writers combed through relevant literature for references, however they only included researches covering the years from 2002 to 2024. Due of lack of translation-related sources, documents in languages other than English were excluded. Also, works in progress, unpublished publications, abstracts from conferences, and dissertations that did not form part of broader scientific investigations were excluded.

Conclusion: LNG-IUS releases a consistent dose of levonorgestrel directly into the uterus, leading to endometrial thinning, glandular atrophy, and restoration of normal endometrial histology. Studies have demonstrated high regression rates, with up to 93% histological resolution within 12 months of insertion. Compared to oral progestins, LNG-IUS offers enhanced efficacy, fewer systemic side effects, improved compliance, and additional contraceptive benefits. In perimenopausal women, LNG-IUS serves as a non-surgical, fertility-sparing treatment, with a favorable safety profile. Although, some concerns have been raised regarding its association with breast cancer, current evidence remains inconclusive and requires further investigation. Its role in atypical hyperplasia is still being explored. However, it may be considered in selected cases where hysterectomy is contraindicated or maintenance of fertility is wanted. Given its high therapeutic efficacy, ease of use, & case acceptability, levonorgestrel-releasing intrauterine system is suggested as a 1st-line management for non-atypical endometrial hyperplasia & holds promise as a conservative option in broader clinical contexts.

Keywords: Endometrial hyperplasia, Non-atypical hyperplasia, Levonorgestrel-releasing intrauterine system, Hormonal therapy.

INTRODUCTION

Endometrial hyperplasia

EH is a prevalent disorder characterized histologically by an unusual overgrowth of glands of endometrium in uterus. It is clinically essential to identify the disorder as an indicator & precursor of endometrial adenocarcinoma, the most prevalent gynecologic malignancy in American females [(1)].

The endometrium undergoes usual alterations during menstruation in response to progesterone & estrogen. Estrogen induces the endometrial lining proliferation, leading to its thickening. Following ovulation, the corpus luteum synthesizes progesterone. If gestation happen, progesterone maintains the endometrium through promoting distinguishing & decreasing proliferation. If pregnancy doesn't happen, the release of progesterone declines, permitting the shedding of the uterine lining [(2)].

In endometrial hyperplasia, unopposed estrogen, characterized by absence of progesterone, leads to the glands of endometrium proliferation, resulting in an elevated gland-to-stroma ratio.

Consequently, endometrial hyperplasia impacts females experiencing absent or intermittent ovulation, as observed in polycystic ovarian syndrome (PCOS), or those with elevated circulating estrogen concentrations after menopause (e.g., obesity, hormone replacement therapy). The predominant clinical manifestation of hyperplasia is abnormal uterine bleeding (AUB), necessitating assessment of diagnosis in post-menopausal females. The cornerstone of hyperplasia treatment is the identification or avoidance of endometrial tumor [(1)].

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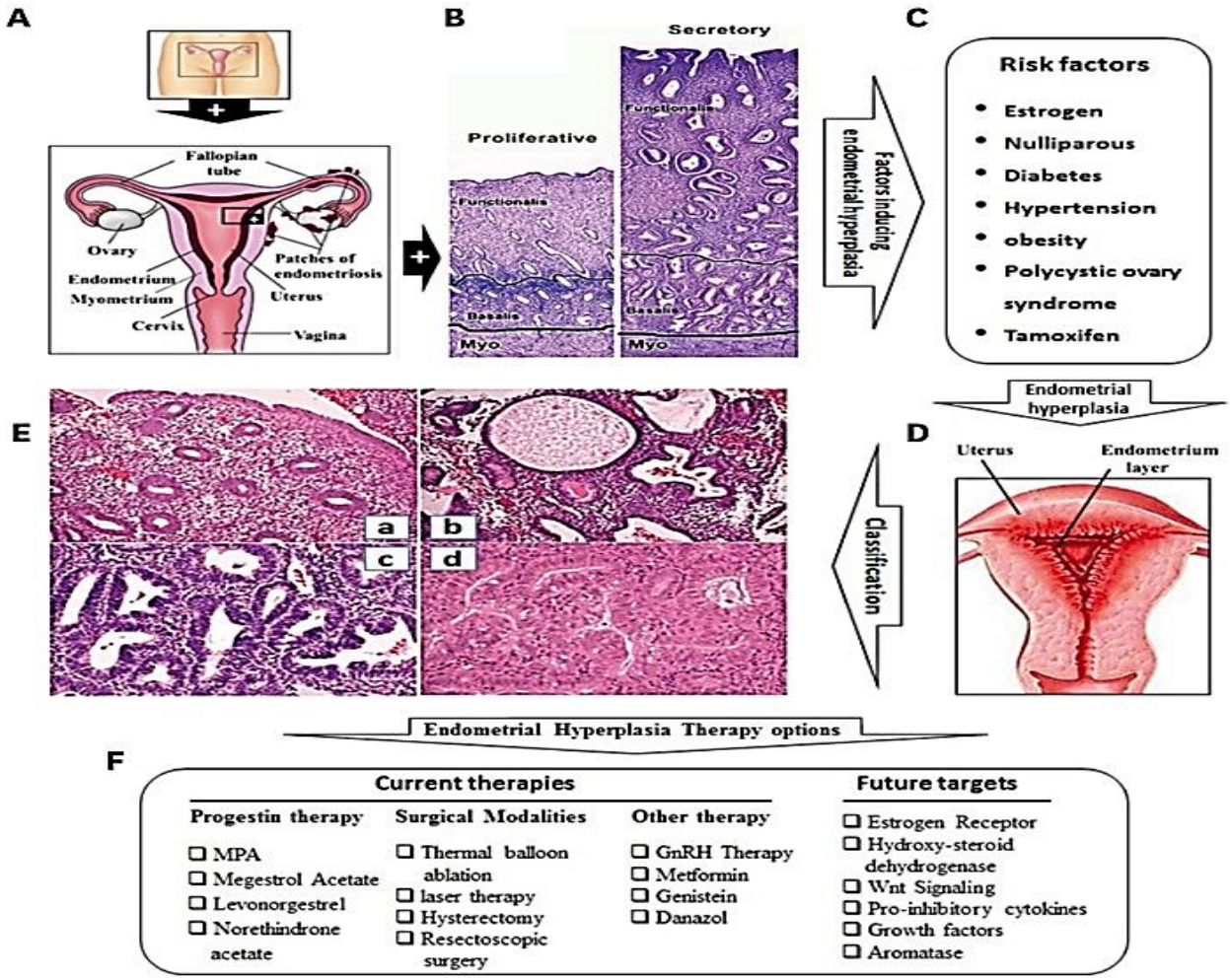

Figure (1): Endometrial hyperplasia, risk factors, categorization & management choices. (A) The cross-sectional view of uterus exhibiting endometrium. (B) E & H staining of endometrium at secretory & proliferative stage of endometrium. (C) Risk factors related to EH. (D) The cross-sectional view of uterus exhibiting proliferative endometrium & the E & H staining of endometrium hyperplasia demonstrating unusual elevation of glands of endometrium. (E) E & H-stained section of endometrium: (a) proliferative endometrium; (b) simple hyperplasia; (c) complicated hyperplasia; & (d) complicated unusual hyperplasia. (F) Various therapeutic choices of endometrial hyperplasia. MPA, medroxy-progesterone acetate [3].

Etiology and risk factors: An additional of estrogen, unopposed through progesterone, whether exogenous or endogenous, is considered as the main etiological factor in all endometrial carcinoma & EH. Estrogen promotes the proliferation of endometrium through attaching to estrogen receptors (ER) located in the nucleus of endometrial cells. Recognized risk factors for endometrial hyperplasia indicate this cause [4].

Obesity & HRT are regarded as reversible risk factors. Females after menopause managed with estrogen replacement therapy (ERT) devoid of progestins face a higher possibility of endometrial hyperplasia. The possibility of endometrial hyperplasia rises ten times with every decade of estrogen replacement therapy utilization. Obese females [Body mass index (BMI) > 30 kg/m^2) exhibit approximately four times rise in the frequency of unusual endometrial hyperplasia because of increased peripheral conversion of androgens to estrogen in fat tissue, together with irregular anovulatory cycles. Tamoxifen, a selective estrogen receptor modulator (SERM), is utilized in the management of ERα-positive both advanced & primary tumors of the breast. It results in endometrial hyperplasia, the formation of endometrial polyps, unusual bleeding from the vagina, & endometrial carcinoma because of its estrogenic impact on the endometrium [5]. As well as estrogenic induction of the endometrium, other components as infection & immunosuppression might additionally be included in the progress of endometrial hyperplasia [6].

Genetic changes such as microsatellite instability (MSI), K-ras mutations, PTEN mutations, PIK3CA mutations, beta-catenin mutations, & functional single nucleotide polymorphisms (SNPs) been identified in lesions of endometrium. Endometrial inflammation disrupts the equilibrium of the cytokine system, resulting in the majority of cases of endometrial hyperplasia.

Inflammation results in a reduction in proliferating cell nuclear antigen (PCNA), tumor necrosis factor-α (TNF-α), & epithelial growth factor (EGF) messenger ribonucleic acid. Also, elevating the synthesis of insulin-like growth factor-1 receptor (IGF-1R) & Fas messenger ribonucleic acid. Glandular cystic hyperplasia is characterized by reduced expression of TNF receptor 1, IL-12 genes & interleukin-1β (IL-1β). The expression of the IGF-1 gene is diminished only in adenomatous hyperplasia [(3)].

The risk factors for endometrial hyperplasia & endometrial carcinoma vary for reproductive variables. Parity is shown as protective against endometrial carcinoma but not against endometrial hyperplasia. The prolonged usage of oral contraceptives has certain defensive impact [(4)].

Table (1): Risk factors for the progress of EH [(7)].

Risk factor group	Risk factor
Non-modifiable	Age above thirty-five years Family history Caucasian ethnicity
Menstrual	Postmenopausal state Extended perimenopause Null parity Early menarche/late menopause
Co-morbid conditions	Diabetes mellitus Functional tumours, e.g., granulosa cell Obesity Polycystic ovarian syndrome Lynch syndrome/hereditary non-polyposiscolorectal cancer (HNPCC)
Iatrogenic	Prolonged Tamoxifen treatment Exogenous estrogen exposure Estrogen only hormone replacement therapy
Others	Genetic mutations Smoking

Epidemiology

Endometrial carcinoma is the predominant gynecologic cancer in developed countries, the 4th major etiology of tumor & 6th etiology of tumor mortality in females. Endometrial tumor in the United States is increasing, with determined frequency of 66,200 patients & 13,030 mortalities in 2023 [(8)]. The frequency of endometrial carcinoma has risen in several countries during recent years, a trend that is hypothesized to be because of the increasing occurrence of obesity, in addition to shifts towards delaying childbearing. Endometrial hyperplasia is a known precursor lesion of the predominant form of endometrial carcinoma (endometrioid), & its identification provides chances for prevention. Early detection & management may efficiently decline the frequency of endometrial carcinoma [(9)].

Diagnosis: EH is frequently suspected in females exhibiting abnormal uterine bleeding (AUB). Over ninety percent of cases with endometrial hyperplasia experience AUB. Nonetheless, diagnostic validation necessitates histological examination of endometrial tissue [(10)].

1. Transvaginal Ultrasonography:

Transvaginal ultrasonography is regarded as a screening method for assessing unusual hemorrhage from the vagina because of its capability to describe endometrial pathology. The extensive accessibility, cost-efficacy, & superior safety profile are the most essential benefits. In females after menopause, a thickness of endometrium above four millimeters is deemed unusual. In asymptomatic postmenopausal & premenopausal females, endometrial thickness isn't definitive, whereas anomalies in the endometrial stripe, like cystic alterations or heterogeneity to the endometrium, might be critical for the identification of endometrial hyperplasia [(11)].

Ultrasound reveals hyperplastic endometrium as thick & hyperechoic, with a morphologically homogeneous microcystic or regular appearance. Nevertheless, presents a widespread range of diversity. The interface among the myometrium & endometrium is regular & clearly defined, frequently revealing the echo median, which permits the differential identification of endometrial polyps, which typically cause distortion in the latter case. Ultrasound can't differentiate between adenomatous hyperplasia & cystic glandular hyperplasia. The differential identification among a well-distinguished adenocarcinoma that doesn't infiltrate the myometrium & endometrial hyperplasia is similarly impossible. Patients of multifocal hyperplasia are additional present: The ultrasound image is marked by a homogenous endometrial attendance or marked by internal cystic gaps that vary in size & regularity. The latter disorder has issues in the differential identification of endometrial carcinoma & endometrial polyps. The investigation utilizing color Doppler is recommended as a further criterion in the differential identification of malignant illness (signs of vascular hyperplasia are limited, predominantly regular & peripheral). The endometrial polyp is predominantly identified as a vascular axis. In carcinomas, the vascular architecture is chaotic & the color Doppler investigation illustrates this chaos. Appropriate identification & staging of EH & cancers is only histological. It is essential to perform a visual direct biopsy on suspicious endometrial regions [(10)].

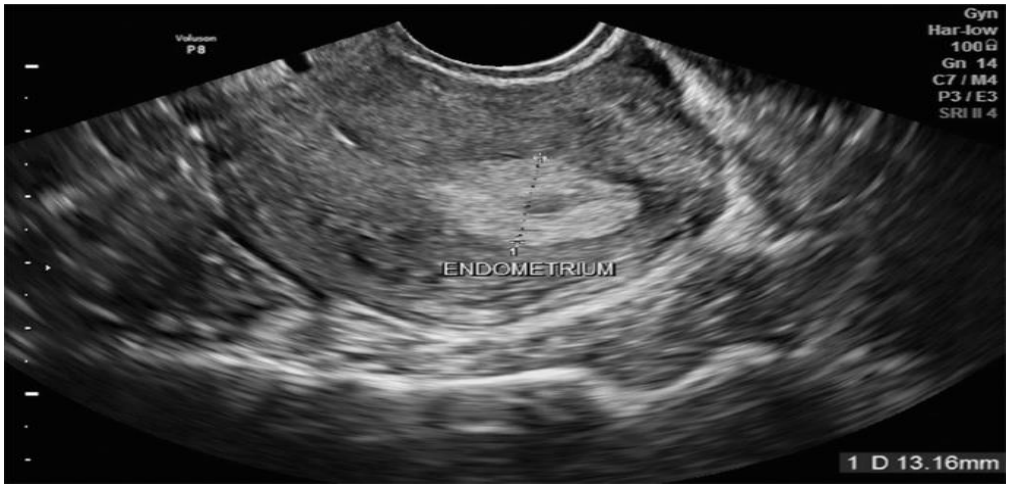

Figure (2): EH as imaged through transvaginal sonography in females after menopause. Thickness of endometrium 13.6 millimeters [(4)]

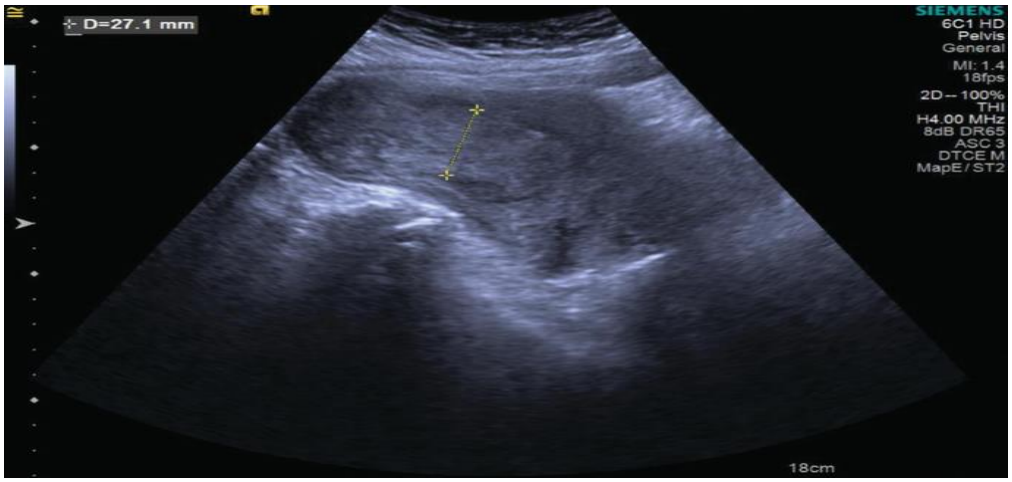

Figure (3): Endometrial thickness as imaged through transabdominal sonography in unmarried case on tamoxifen (longitudinal view). Thickness of endometrium 27 millimeters [(4)].

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2. Three-dimensional Ultrasonography:

Research indicates that three-dimensional ultrasonography & particularly three-dimensional power Doppler measurements may effectively differentiate among lesions of benign endometrium & endometrial carcinoma in females experiencing abnormal uterine bleeding after menopause. Cases with malignant endometrium exhibit significantly elevated volume of endometrium, thickness of endometrium, vascularization flow index, & endometrial vascularization index compared to those with benign endometrium [(12)].

3. Hysteroscopy:

Morphological criteria serve as hysteroscopic markers of EH. These characteristics haven't been determined according to scientific proof caused by regulated randomized clinical trials (RCTs). The characteristics of morphology obtained from hysteroscopic examination are personal, operator associated, & poor reproducibility. The sensitivity of hysteroscopy in diagnosing endometrial hyperplasia doesn't exceed seventy-eight percent [(13)].

Hysteroscopy is a technique utilized for cases with AUB requiring biopsy & aids to direct below visual central biopsy reliability & compliance alterations. EC & EH are impacting a monolayer epithelium (endometrium). All cases exhibit anomalies & morphological changes associated with endometrial malignancy & hyperplasia. Hysteroscopy frequently fails to provide a differential identification; however, it can identify a "atypical area" for biopsy in hundred percent of cases [(10)].

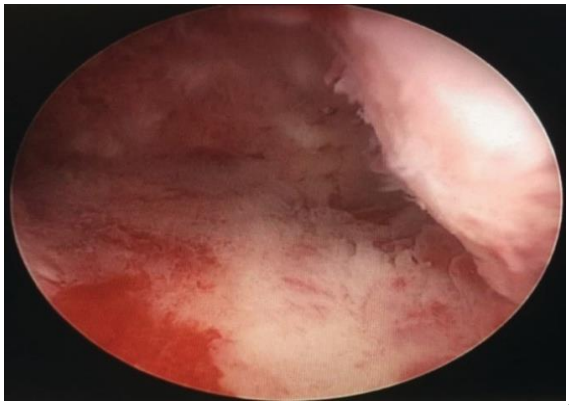

Figure (4): Usual endometrium on hysteroscopy [4]

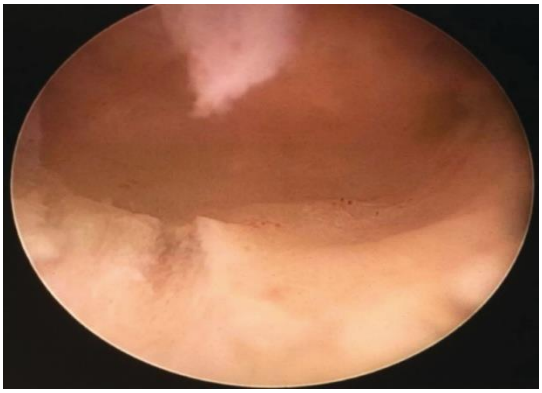

Figure (5): Endometrial hyperplasia on hysteroscopy [4]

Management Options

1. **Medical management:** Progestins, SERM, gonadotropin-releasing hormone (GnRH) antagonists, sulfatase inhibitors, aromatase inhibitors, metformin, protein-tyrosine kinases inhibitor (genistein) & synthetic androgen (danazol) are all examples of hormonal therapies that are utilized in the treatment of endometrial hyperplasia [14].

1.1. Progestin therapy: Progestins, artificial progestogens that simulate usual progesterone, are predominantly utilized to promote the EH regression in females with non-atypical endometrial hyperplasia, those seeking fertility, those refuse operation, or those with contraindications to operations because of significant medical comorbidities. The therapeutic goals of progestin treatment include the total regression of endometrial hyperplasia, return to usual endometrial function, & the avoidance of endometrial carcinoma. Progesterone induces secretory alterations in the usual endometrium. It induces these impacts through raising the degradation of ER & elevating the activity of the enzymes sulfotransferase & 17-b-hydroxysteroid dehydrogenase, thus reducing concentrations of estrogen. It induces apoptosis, resulting in reduced glandularity & decreases angiogenesis in the myometrium. This ultimately results in the thinning & sloughing of the endometrium [14].

Progestin treatment is contraindicated in individuals with a past or current history of thromboembolic illnesses or stroke, severe hepatic failure, suspected or recognized cancer of progesterone receptor-positive tumor of the breast, vaginal hemorrhage of unrecognized cause, pregnancy, & identified hypersensitivity to progestins. Multiple methods of giving are available, including oral, intramuscular, vaginal, & intrauterine devices [3].

Unfortunately, the ideal progestin regimen & period remain unexamined & prolonged monitoring following management hasn't been sufficiently documented. 60% of females undergoing ERT with atypical hyperplasia reacted positively to progestin therapy & recovered. The response to progestin treatment typically starts around ten weeks & ends by six months. Cyclic progestin exhibits a lower rate of regression for endometrial hyperplasia in comparison with permanent oral progestin or levonorgestrel intrauterine device. Prognostic variables encompass a reduced gland-to-stroma ratio, absence of cytologic atypia, reduced mitotic activity & various alterations in histology, cytoplasm, or architecture [14].

A. Megestrol acetate (MA)—is a steroidal progestin that is efficient in endometrial hyperplasia due to its progesterone-like & antigonadotropic impacts. It is regarded as a "chemotherapeutic agent," however more accurately categorized as a robust progestin. Dosages range from 160 to 320 milligrams per day. At these dosages, the advantageous impacts on the endometrium are optimized, with little impacts on lipid profiles or the concentrations of blood glucose [3].

B. Medroxyprogesterone acetate (MPA)— is an artificial steroidal progestin frequently utilized in HRT for females after menopause, aiding in the prevention of endometrial hyperplasia. The standard dosage administered is ten milligrams per day permanently for six weeks. or two weeks per month for three months, which is considered safer & more satisfactory compared to permanent treatment. If the response is inadequate, treatment may be prolonged for an additional three months [3].

C. Norethindrone acetate/norethisterone acetate (NETA)— is an artificial steroidal progestin that is intended for oral administration and possesses both antiestrogenic & antiandrogenic impacts. In postmenopausal females who are using hormonal replacement therapy, it was demonstrated to decrease the endometrial hyperplasia possibility. A daily intake of fifteen milligrams is advised [3].

D. Micronized progesterone—isn't suggested for use as the initial management for endometrial hyperplasia since it is a relatively weak progesterone. Only females who are at a reduced possibility for development as well as those who are unable to tolerate more strongly synthetic

progestins or who refuse to use a levonorgestrel intrauterine device are permitted to take it in doses ranging from 200 to 300 milligrams per day. When it comes to the management of endometrial hyperplasia, there was no research conducted on the usage of vaginal micronized progesterone. Theoretically, it is possible to utilize it as a prolonged therapy because it has the potential to achieve great endometrial concentrations because of its local impacts [(15)].

E. Levonorgestrel (LNG)— is a 2nd-generation progestin (artificial progestogen) & the IUD consisting of levonorgestrel presents an appealing choice for the endometrial hyperplasia management. It produces a permanent quantity of levonorgestrel within the uterus & efficiently inhibits the estrogenic impact [(4)]. The levonorgestrel 52/5 begins with an initial dosage of twenty micrograms per day, which decreases to around 10 mcg/day after 5 years. The levonorgestrel intrauterine device initially causes irregular hemorrhage, similar to other progestin-only therapies, nevertheless most females ultimately have amenorrhea or light tolerable hemorrhage. Optimal results in the medical treatment of endometrial hyperplasia necessitate the utilization of levonorgestrel intrauterine device for a duration of up to five years [(16)]. The levonorgestrel intrauterine device is accessible in reduced daily doses (13.5, 17.5, & 18.6 micrograms per day) & is available in three-to-five-year formulations. However, these hasn't been examined in females with endometrial hyperplasia to identify if the reduced progestin dosage is as efficient as the levonorgestrel 52/5.

Comparison of oral progestins with LNG-IUD— The levonorgestrel intrauterine device exhibits elevated intrauterine however reduced systemic concentrations of progestin. Consequently, it has a robust impact on the endometrium repeatedly without resulting in side effects like pain of breast, gaining weight & mood alterations. As well as enhanced efficiency, it provides long-acting contraceptive, eliminates the necessity for daily dose & demonstrates superior tolerance in comparison with oral progestins. Additional restrictions of the levonorgestrel intrauterine device include a possibility of uterine perforation of 1 in 1000 & the necessity for invasive insertion into the uterus. An insignificant variance has been observed in the rate of irregular vaginal hemorrhage with the levonorgestrel 52/5 in comparison with oral progestins [(16)].

Administrating progestins orally are favored over levonorgestrel intrauterine devices in females that reject or can't endure an intrauterine device due to side effects (e.g., dysmenorrhea), those with uterine conditions, which make the retention or placement of an intrauterine device (e.g., severe deformity of the cavity of uterus because of congenital or fibroids abnormalities) & females deciding to become pregnant immediately following a complete therapeutic reaction. Progestins aren't suggested during gestation & the case may discontinue oral drug without necessitating a clinician to eliminate the device, as is the case with an intrauterine device [(15)].

F. Progestin injections and implants—Depot medroxyprogesterone acetate (DMPA) is a long-acting progestin, which gives contraception & needs only 4 injections annually. Its efficacy in treating endometrial hyperplasia hasn't been thoroughly investigated. One research showed that intramuscular depot medroxyprogesterone acetate (150 milligrams every three months) was more effective compared to NETA (fifteen milligrams daily for fourteen days each cycle) in managing nonatypical endometrial hyperplasia. Concerning side effects, breast pain & nausea were more prevalent with NETA, but amenorrhea was more common with depot medroxyprogesterone acetate [(15)].

Prevalent progestins side effects encompass nausea, gaining weight, vomiting, headache, irregularities of menstruation, & occasionally depression & hypertension. The frequency of embolism & venous thrombosis might be somewhat elevated. Oral progestins are related to systemic side effects & poor compliance, which may restrict their general effectiveness. Annoying side effects might need a dosage adjustment or a transition to a various progestin treatment. For females on systemic progestins, alter to the levonorgestrel intrauterine device may be regarded [(4)].

Approximately twelve to fifty-five percent of females with endometrial hyperplasia don't respond to progestin treatments. The response to progestins is influenced by the age of the case, the grade & form of hyperplasia, the number of progesterone receptors, insulin resistance, the activity of co-repressors & co-activators & the changed activity of epithelial growth factor receptor & TGF-α in cells of endometrial glandular. Progestin resistance to treatment may infrequently arise from paracrine impacts. The histological response of atypical endometrial hyperplasia/endometrial intraepithelial neoplasia glands is closely related to the decidual reaction in the stroma, so the probability of a paracrine impact is convincing. Therefore, frequent monitoring & endometrial biopsy are advised for cases whereas on progestin treatment. The use of HE4 as a new tissue indicator for expecting therapeutic reaction & resistance of progestin in endometrial hyperplasia was investigated & demonstrated to be efficient [(17)].

2. Therapy other than progestins

a. Ovulation induction— In females of reproductive age, stimulation of the ovulation performed aromatase or

clomiphene inhibitors will result in exposure to endogenous progesterone, corpus luteum production, & the resolution of endometrial hyperplasia in certain females. Pregnancy is greatly unpredicted in the context of persistent endometrial hyperplasia. Thorough monitoring is required to validate regression of endometrial hyperplasia. This method is advised for females with endometrial hyperplasia without atypia who wish to conceive [(15)].

b. Metformin— Endometrial hyperplasia is related to metabolic syndrome, obesity, polycystic ovarian syndrome, type II diabetes, & insulin resistance that have a mitogen impact on the endometrium. Metformin (N, N-dimethylbiguanide) is a biguanide that reduces gluconeogenesis in the liver, hence diminishing insulin resistance. Prolonged progestin treatment results in diminished concentrations of PR. Metformin stimulates progesterone receptors expression in cells of the endometrium, aiding in overcome progestin resistance treatment. Metformin is particularly beneficial for obese females, since it aids in weight reduction, subsequently leading to a reduction in the peripheral conversion of androgen to estrogen & a superior response to progestins. Metformin is currently being investigated in conjunction with levonorgestrel intrauterine device & megestrol acetate [(16)].

c. GnRH therapy—Gonadotropin-releasing hormone agonists decrease estrogen through decreasing hypothalamic-pituitary-ovarian axis, hence having an antiproliferative impact on cells of the endometrium. Females with endometrial hyperplasia, regardless of atypia, may receive gonadotropin-releasing hormone at a dosage of one ampule (3.75 milligrams) intramuscularly monthly for a duration of six months. The research utilizing gonadotropin-releasing hormone & tibolone (A synthetic steroid exhibiting all progestagenic & estrogenic impacts) for the endometrial hyperplasia management demonstrated that while a complete response has been observed in all cases, repeat happened within two years in nineteen percent following the discontinuation of the treatment. In an additional research, gonadotropin-releasing hormone agonists & levonorgestrel intrauterine device have been utilized in conjunction with a rate of release of 19.5 micrograms per day for five years (Mirena; levonorgestrel 52/5) to efficiently manage twenty-four premenopausal females diagnosed with either atypical endometrial hyperplasia or early-stage endometrial carcinoma [(3)].

d. Danazol— It is an artificial androgen that induces endometrial atrophy by its capability to release hypoandrogenic & hypoestrogenic status. It was demonstrated to be efficient for the endometrial hyperplasia management, with a relapse rate of about eight to nine percent. The side effects of oral danazol including gaining weight, hirsutism, acne & muscular cramps restrict its application for endometrial hyperplasia, that may be reduced to some degree through utilizing a danazol-containing intrauterine device [(15)].

e. Genistein— It is an isoflavonoid derived from soy products. It reduces the concentrations of estrogen through decreasing topoisomerase & protein-tyrosine kinases II. The treatment of endometrial hyperplasia has yet to be established pending further clinical trials [(3)].

3. Surgical management

Operative choices presently encompass hysterectomy, without or with bilateral salpingo-oophorectomy (BSO), performed using vaginal, abdominal, or minimally invasive techniques, like robotic or laparoscopic approaches. Overall extrafascial hysterectomy is the technique of option giving a definitively evaluating of a concurrent endometrial carcinoma & efficiently managing endometrial hyperplasia. Supracervical hysterectomy isn't recommended because to the possibility of local extension of endometrial cancer into the cervix, therefore increasing the possibility of residual illness [(6)].

Uterine morcellation must be prevented because of the possibility of disseminating concurrent endometrial carcinoma. The drawbacks of vaginal hysterectomy encompass the technical challenges in ovarian elimination, & complete operative staging, if necessary, is unfeasible. Throughout the hysterectomy, gross inspection using both frozen & usual section analysis, particularly in patients of increased possibility, must be conducted to assess for endometrial carcinoma. The discrepancy among the frozen-section analysis of tissue of the endometrium & the last identification depending on the continuous section is concerning [(18)].

In spite of endometrial sampling before operation & assessment during operation, certain females with atypical endometrial hyperplasia will have endometrial carcinoma identified only upon final pathological assessment. Females with elevated-risk factors must be clarified about the necessity of further staging operations if endometrial carcinoma is detected, irrespective of the operative method. After a total hysterectomy, if the specimen shows no evidence of endometrial carcinoma, continued monitoring for endometrial hyperplasia is unnecessary [(4)].

For females receiving hysterectomy as management for atypical endometrial hyperplasia, the option of bilateral salpingo-oophorectomy must be taken following weighing the possibility of early menopause & possible risks of oophorectomy against the possibility of a 2nd operation if endometrial carcinoma is detected after the operation. Certain females could decide for bilateral salpingectomy alone rather than oophorectomy, maybe to prevent ovarian, fallopian tube, or peritoneal tumors (level three or four proof). Endometrial ablation utilizing electric or thermal cautery devices isn't suggested for the

management of atypical endometrial hyperplasia/endometrial intraepithelial neoplasia. No techniques exist to verify the thoroughness of ablation. Furthermore, due to following adhesions, the cavity might be partially unavailable for monitoring following ablation [6].

Levonorgestrel-releasing intrauterine system

The levonorgestrel-releasing intrauterine system (LNG-IUS) was initially introduced in Finland in 1990. Mirena, the 1st marketed levonorgestrel-releasing intrauterine system, comprises fifty-two milligrams of levonorgestrel, that is produced into the cavity of the uterus at a rate of twenty µg per day over a duration of 5 years. Subsequent to the introduction of levonorgestrel-releasing intrauterine system fifty-two milligrams (Mirena). Additional forms of levonorgestrel-releasing intrauterine system, Jaydess & Kyleena, were additional released in the economic market. Kyleena comprises 19.5 milligrams of levonorgestrel, while Jaydess, additional marketed as Skyla in the United States of America, comprises 13.5 milligrams of levonorgestrel [19]. Every of these levonorgestrel-releasing intrauterine systems produce a contraceptive impact through thickness of the cervical mucosa & thinning of the endometrium. The foreign body response induced through the device might have a role in the contraceptive impact [20].

In spite of its permitted contraceptive impacts in several researches, discomfort or hesitation concerning the utilization of an intrauterine device may influence its approval among females, varying by age. Misconceptions concerning intrauterine devices, like the potential to cause pelvic inflammatory illness or infertility, as well as the comparatively elevated frequency of device expulsion, were documented in nulliparous & adolescents females [21]. Nevertheless, the safety of intrauterine devices in nulliparous & adolescents females is supported through current guidelines, in addition to in perimenopausal females. Perimenopause includes the period of duration throughout that physiological alterations mark development toward a female's last menstrual period. These alterations stimulate different clinical symptoms like irregular hemorrhage, vasomotor symptoms & mood alterations [22].

The utilization of levonorgestrel-releasing intrauterine systems in perimenopausal females has a distinct aim compared to its utilization in adolescents. The frequency of different gynecologic disorders rises in perimenopausal females, necessitating the selection of options for therapies with regard to the time of menopause. The majority of benign gynecological illnesses are typically asymptomatic following menopause. Consequently, transient therapy choices depending on the symptoms of the case, rather than definitive & operative management modalities, may be used as the 1st-line of treatment for perimenopausal females. In contrast to levonorgestrel-releasing intrauterine system 19.5 milligrams (Kyleena) & levonorgestrel-releasing intrauterine system 13.5 milligrams (Jaydess), levonorgestrel-releasing intrauterine system fifty-two milligrams (Mirena) has demonstrated non-contraceptive advantages in other disorders, like decreasing of dysmenorrhea, prevention & management of endometrial hyperplasia & management of heavy menstrual bleeding (HMB) [19].

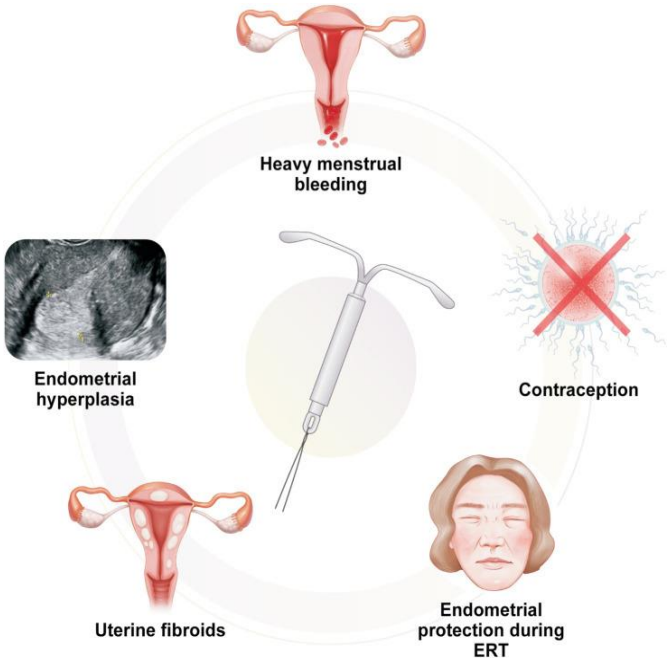

Figure 6. Overview of LNG-IUS usage in perimenopausal females. ERT: estrogen replacement therapy [20].

Efficacy of the LNG-IUS as treatment for EH

EH is a spectrum of irregular morphological alterations characterized by the unusual endometrial glands' proliferation, leading to an elevated gland-to-stromal ratio in comparison with the endometrium in the proliferative stage of the menstrual cycle. Numerous histological categorization techniques, which were suggested to this point purpose at associating the cytological & architectural characteristics of endometrial hyperplasia with the possibility of development to endometrioid carcinoma. Endometrial hyperplasia is categorized into 2 classes: Atypical hyperplasia/endometrial intraepithelial neoplasia & hyperplasia without atypia [3].

Currently updated protocols have suggested that the levonorgestrel-releasing intrauterine system must be utilized as the 1st-line management for EH without atypia [23]. In cases of females with atypical hyperplasia desiring to maintain fertility, the levonorgestrel-releasing intrauterine system is particularly suggested as the 1st-line management. Nonetheless, there has been no

documentation about the utilization of the levonorgestrel-releasing intrauterine system in pre-menopausal females diagnosed with atypical EH. The frequency of endometrial carcinoma rises with age, & EH is a recognized lesion before cancer. Consequently, the management of endometrial hyperplasia is particularly crucial for perimenopausal females. The development rate to tumor in endometrial hyperplasia without atypia has been determined to be 2.6 percent annually [(24)].

Consequently, the utilization of levonorgestrel-releasing intrauterine system, identified as the most efficient medication management, encompasses various factors to be regarded as the 1st-line management. The development rate for endometrial hyperplasia with atypia is very high at 8.2 percent a year. In this case, hysterectomy is the standard therapies & there is no information about the impact of levonorgestrel-releasing intrauterine system on EH with atypia in pre-menopausal females. Nonetheless, when regarding the impact in females of reproductive age, it may be regarded as equally efficient in perimenopausal females. If preservation of fertility is sought, it could be regarded in cases of early endometrial carcinoma, especially for cases who have previously received freezing of oocyte or are regarded donation of oocyte from younger females [(20)].

Efficacy of the levonorgestrel-releasing IUS

The intrauterine device, generally is among the most efficient types of contraceptives now accessible, exhibiting a global cumulative rate of pregnancy below two percent over 5 years. The levonorgestrel-releasing intrauterine system especially is probably the most efficient intrauterine device accessible depending on several researches indicate its global cumulative rate of pregnancy is below 0.5 percent. A substantial randomized regulated experiment involving 2,244 females over 7 years demonstrated a rate of pregnancy of 1.1 percent with the levonorgestrel-releasing intrauterine system, in comparison with 1.4 percent with the TCu380. In 2 additional 7 years monitor researches involving 293 & 82 females correspondingly, no pregnancies occurred among females utilizing the levonorgestrel-releasing intrauterine system. A Cochrane review in 2004 demonstrated that the levonorgestrel-releasing intrauterine system is equally efficient as copper intrauterine devices with a copper surface area over 250 millimeters square, & more efficient compared to those with a surface area less than 250 millimeters square [(25)].

The LNG-IUS is an effective choice for females to select immediately following an abortion. Numerous researches have demonstrated that copper-releasing intrauterine devices are both efficient & may be safely within this period. Limited research was performed particularly the levonorgestrel-releasing intrauterine system in this context. Yet, findings indicate it is at minimum as efficient as the copper intrauterine device. A levonorgestrel-releasing intrauterine system can be safely placed immediately following either stimulated abortions or simple spontaneous [(26)].

The levonorgestrel-releasing intrauterine system may be efficiently implanted immediately postpartum, however the expulsion possibility is elevated compared to period insertion. Research involving nineteen females who underwent post-placental levonorgestrel-releasing intrauterine system, characterized by insertion within ten min of placental expulsion, revealed a rate of expulsion of 10.5 percent & no infection. No researches particularly investigate the timing of levonorgestrel-releasing intrauterine system insertion postpartum. However, research involving a copper-releasing intrauterine device indicates that post-placental intrauterine device insertion has a significantly reduced rate of expulsion (22.6 percent partial & 14.3 percent complete) compared to early postpartum insertion, recognized as occurring ten minutes to seventy-two hours following placental delivery, after one year (51.2 percent partial &18.6 percent complete). All rates were significantly greater than those of period insertion (3.1 percent partial & 3.8 percent complete). No perforations occurred in any postpartum group, but the interval groups exhibited a perforation rate of 2.3 percent [(27)].

CONCLUSION

The insertion of the levonorgestrel-releasing intrauterine system is an acceptable & relatively simple choice for post-placental insertion, provided the females are adequately advised about the elevated possibility of expulsion against period insertion, have appropriate guidance on examining the intrauterine system strings & have proper clinical monitoring. In numerous reduced-resource settings, the cervix (Or uterus during Cesarean delivery insertions) is accessible at the time of delivery & cases are frequently positioned in lithotomy. Post-placental insertion might decrease difficulties to period insertions, like the absence of sounds, speculae, examination tables, tenacula, & congested clinics [(28)].

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