Review

Therapeutic Options for Management of Endometrial Hyperplasia: An Update

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**Abbreviations:**

Body mass index (BMI), chemokine (C-C motif) ligand 2 (CCL2), confidence interval (CI), danazol containing intrauterine device (D-IUD), endometrial cancer (EC), endometrial hyperplasia (EH), endometrial intraepithelial neoplasia (EIN), estrogen receptor (ER), gonadotropin-releasing hormone (GnRH), levonorgestrel-impregnated intrauterine device (LNG-IUS), medroxy-progesterone acetate (MPA), megestrol acetate (MA), levonorgestrel (LNG), odds ratio (OR), polycystic ovarian syndrome (PCOS), selective estrogen receptor modulators (SERMs), World Health Organization (WHO), continuous-combined hormone replacement therapy (CCHRT), progestron receptor (PR), Vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), mechanistic target of rapamycin (mTOR), human epidermal growth factor receptor 2 (HER-2/neu), insulin-like growth factor 1 receptor (IGF-1R) and V-myc avian myelocytomatosis viral ncogene homolog (c-MYC), tumor necrosis factor-α (TNF-α), proliferating cell nuclear antigen (PCNA), epithelial growth factor (EGF), tumor necrosis factor receptor 1 (TNF-R1), interleukin-1β (IL-1β), insulin-like growth factor-1 (IGF-1), nuclear factor-κB (NF-κB), phosphatase and tensin homolog (PTEN).
Abstract

Endometrial hyperplasia (EH) is comprised of a spectrum of changes in the endometrium ranging from a slightly disordered pattern that exaggerates the alterations seen in the late proliferative phase of the menstrual cycle to irregular, hyperchromatic lesions that are similar to endometrioid adenocarcinoma. Generally, EH is caused by continuous exposure of estrogen unopposed by progesterone, polycystic ovary syndrome, tamoxifen or hormone replacement therapy. Since it can progress, or often occur coincidentally with endometrial carcinoma, EH is of clinical importance, and the reversion of hyperplasia to normal endometrium represents the key conservative treatment for prevention of the development of adenocarcinoma. Presently, cyclic progestin or hysterectomy constitutes the major treatment options for EH without atypia or with atypia, respectively. However, clinical trials of hormonal therapies and definitive standard treatments remain to be established for the management of EH. Moreover, therapeutic options for EH patients who wish to preserve fertility are challenging and require nonsurgical management. Therefore, future studies should focus on evaluation of new treatment strategies and novel compounds that could simultaneously target pathways involved in the pathogenesis of estradiol-induced EH. Novel therapeutic agents precisely targeting the inhibition of ER, growth factor receptors, and signal transduction pathways are likely to constitute an optimal approach for treatment of EH.

Key words: Endometrial Hyperplasia; Estrogen Receptor; Progestin; Therapy.
Introduction:

The endometrium, the innermost glandular layer of the uterus, is a dynamic tissue that goes through a series of alterations (proliferation, secretion and menstruation/shedding) during the menstrual cycle in a woman’s reproductive years [1]. This cyclic phase involves a complex interaction between the two female sex hormones, estradiol and progesterone (Figure-1). Estrogen promotes epithelial cell proliferation resulting in thickening of the uterus, while progesterone encourages epithelial cell differentiation and the secretory phase of the endometrial cycle [2, 3]. The fine equilibrium between endometrial proliferation and apoptosis is maintained by an intricate process involving a number of factors, including hormonal balance, molecular mechanisms, environment, age, etc.; accordingly, it is prone to various disturbances leading to several endometrial abnormalities [4].

Endometrial hyperplasia (EH) is a pre-cancerous, non-physiological, non-invasive proliferation of the endometrium that results in increased volume of endometrial tissue with alterations of glandular architecture (shape and size) and endometrial glands to stroma ratios of greater than 1:1 [5, 6]. Currently, the incidence of EH is inadequately reported with an approximately estimated incidence of 200,000 new EH cases per year in Western countries [7]. The majority of cases of EH arise in the presence of chronic exposure to estrogen unopposed by progesterone such as in earlier forms of hormone replacement therapy [6]. Overproduction of estrogen by fat cells also contributes to the higher risk of EH and endometrial cancer (EC) in obese women [8, 9]. In addition to inducing proliferation of the uterus [10], estrogen induces morphometric alterations in the uterus that include changes in the type of luminal and glandular epithelia, the number and shape of glands, the gland to stroma ratio, and the morphology of epithelial cells [11, 12].
EH also occurs after menopause, when ovulation stops and progesterone is no longer produced, as well as during perimenopause when women experience irregular ovulation. The most common symptom of EH is abnormal uterine bleeding including, menorrhagia, intermenstrual bleeding, postmenopausal bleeding and irregular bleeding when on hormone replacement therapy or tamoxifen [13-15]. Currently, the treatment approaches for EH are limited, for example hysterectomy or hormone therapy [16]. EH without-atypia is generally treated with progestins [17-19], while hysterectomy is the best treatment option for EH with-atypia [20].

Since EH with-atypia may progress to or coexist with EC [21], it is of clinical importance and should not be ignored. Moreover, conservative treatment with progestins is designed to regress hyperplasia to normal endometrium to prevent subsequent development of adenocarcinoma [22]. However, hormonal management of women with EH has largely been based on descriptions of case studies, while the exact efficacy of hormonal treatment has not been well assessed. The lack of standard and conservative treatment options emphasizes the need for new therapies. In this review, we discuss the etiology and risk factors for EH and the related advancement or existing therapies.

**Classification of endometrial hyperplasia**

Two different systems are commonly used to classify EH, the World Health Organization (WHO) schema [13] and the endometrial intraepithelial neoplasia (EIN) [23, 24] (Table 1). The WHO classification system, which is the most commonly recognized system, use cellular complexity, crowding of the endometrial gland and the presence of cytological-atypia to categorize pathologies as simple or complex hyperplasia, with or without-atypia [15, 25, 26] (Table-1; Figure-1).
The complexity of the WHO classification system has prompted improvement of an alternative system, the EIN. The EIN classifies EH as either benign or hyperplasia, and includes additional EIN and cancer classifications [27]. Cases are categorized as EIN based on architectural gland crowding, altered cytology and maximum linear dimension of the lesion exceeding 1 mm, while excluding cancer and mimics [27-29]. The EIN classification system can easily be applied to routine HE stained sections and is more reproducible, helping clinicians to select treatment options [28, 29]. This system efficiently classifies samples into high and low cancer risk categories. Various other old classifications are summarized in Table-1.

**Risk of progression**

EH represents a continuum of histologically distinct processes, starting from simple-EH without-atypia and then progressing to complex-EH with-atypia, followed by well-differentiated endometrial carcinoma [30] (Figure 1). The presence and severity of cytological-atypia and architectural crowding are key factors defining the risk for progression to carcinoma. Simple hyperplasia shows the lowest risk of cancer progression, and most cases (80%) of this naturally regress [13, 31]. Among patients with atypical hyperplasia, postmenopausal status is associated with the highest risk of progression to adenocarcinoma [16]. Simple hyperplasia is associated with 3% and 8% rates of progression to complex hyperplasia and simple atypical hyperplasia, respectively. Complex hyperplasia has an intermediate risk of progression, which has been shown to regress in most of cases, while EH with cytological-atypia is characterized as direct precancerous lesions and may carry a higher risk of progression to carcinoma [32]. Another study reported progression to EC in 1% of patients with simple hyperplasia, 3% of patients with complex hyperplasia, 8% of patients with simple atypical hyperplasia, and
29% of patients with complex atypical hyperplasia [13]. A recent study reported that 2% of the cases with complex hyperplasia (8/390) progressed to EC and 10.5% into atypical hyperplasia, while 52% of the atypical hyperplasia progressed into EC [33].

**Risk factors:**

Since EH is a precursor to cancer, all risk-factors of EC could be related to EH (Table 2). Postmenopausal, nulliparous and infertile women are at greater risk of developing EH [34, 35]. Diabetes, hypertension and obesity are also associated with increased EH risk [13, 36]. In addition to elevated estrogen levels, obesity causes chronic inflammation that can promote hyperplasia and cancer development [8]. When compared with non-obese women, obese women (BMI >30 kg/m²) exhibited a nearly 4-fold increase in the incidence of atypical-EH. Furthermore, women with a BMI of 40 kg/m² showed a 13-fold increased risk of EH with-atypia and a 23-fold increased risk of EH without-atypia [37].

Postmenopausal women taking estrogen supplements have long been known to be at increased risk of EH if a progestin is not used to oppose estrogen-activity [14]. The risk of developing EH also increases with increasing dose and length of estrogen treatment [38-40]. In a randomized placebo-controlled PEPI (Postmenopausal-Estrogen/Progestin-Interventions) trial, women receiving conjugated equine estrogen alone were more likely to develop simple-EH (28% vs 1%), complex-EH (23% vs 1%), and EH with-atypia (11.8% vs 0%), whereas combining the conjugated equine estrogen with cyclic or continuous progestins protected the endometrium from hyperplastic changes associated with estrogen-only therapy [41].

Several conditions associated with steroid hormone imbalances cause increased risk of EH and EC. Chronic anovulation, early menarche, late onset of menopause and other
conditions associated with increased estrogen levels are also risk factors for EH. Polycystic ovary syndrome (PCOS) associated with anovulation leads to unopposed estrogenic activity on the endometrium [13]. Women with hereditary non-polyposis colonic cancer (Lynch-syndrome) may have complex atypical-EH at an earlier age [42] and altered estrogen levels which affects expression of DNA repair genes [43]. Androgen-secreting tumors of the adrenal cortex may induce the peripheral conversion of androgens to estrogens and is a rare cause of EH [14].

The endometrium is reported to have a balanced cytokine system with numerous correlations at the proliferative and secretory stages of the menstrual cycle. Though inflammation is the most important factor in most hyperplasia conditions, only a few studies have focused on the role of various pro- and anti-inflammatory cytokines in EH pathogenesis. Zhdanov et al., 2003 reported prominent imbalance in the cytokine system in atypical hyperplasia [44]. EH was associated with reduced production of tumor necrosis factor-α (TNF-α), proliferating cell nuclear antigen (PCNA), and epithelial growth factor (EGF) mRNA and enhanced production of Fas mRNA. The expression of tumor necrosis factor receptor 1 (TNF-R1), interleukin-1β (IL-1β), and IL-12 genes was found to decrease only in glandular cystic hyperplasia while the expression of the insulin-like growth factor-1 (IGF-1) gene decreased only in adenomatous hyperplasia [45]. Production of IGF-1 is induced by estradiol and implicated in the estrogen effects on uterine growth [46]. The IGF-1 receptor (IGF-1R) was found to be expressed at higher levels in EH and EC in comparison to proliferative endometrium [47]. Furthermore, TNF-α was demonstrated to be expressed in normal endometrium and in simple and complex hyperplasia, but it was down-regulated in atypical hyperplasia and endometrial carcinoma. The transcription
factor nuclear factor-κB (NF-κB) was also expressed in proliferating endometrium and in EH, but its expression was lower in carcinoma [48].

The most common genetic alterations in endometrial lesions (atypical EH or endometrioid endometrial carcinomas) are microsatellite instability (MSI) [49], PTEN mutations [50], K-ras mutation [51], beta-catenin mutation [52] and PIK3CA mutation [53]. PTEN, is involved in the pathogenesis of endometrial lesions and may precede the development of the MSI [49]. An immunohistochemical study revealed an important role of mismatch repair genes (hMLH1 and hMSH2) in the development of MSI in EC and atypical EH [54]. Patients with diagnosed hyperplasia were reported to have significant genome imbalance [55] and frequent deletions on the short arm of chromosome 8 [56]. Dysregulation of CTNNB1/β-catenin has been observed in atypical EH, complex EH with atypia, and in endometrial intraepithelial Neoplasia [57]. Further mutant alleles of rs1800716 CYP2D6 polymorphisms were associated with increased chance of having double endometrial thickness of ≥5 mm in postmenopausal women on tamoxifen [58]. CYP17 polymorphism had correlation with endometrial atypia and cancer. Significant increase of A1/A1 and a decrease of A1/A2 genotype frequencies have been determined in patients with atypical EH [59]. A recent study showed a role of functional SNPs in the Catechol-O-methyltransferase (COMT), Apolipoprotein E (APOE), and Hemochromatosis (HFE) genes in EH and EC [60].

**Tamoxifen and endometrial hyperplasia risk**

Among selective estrogen receptor (ER) modulators (SERMs), tamoxifen is the primary endocrine agent used to treat ERα-positive primary and advanced breast cancers [61-63]. Tamoxifen has been shown to improve the overall survival for both pre- and post-menopausal patients [64]. The first cases of endometrial carcinoma related to tamoxifen
use were reported in 1985 [65]. Since then, many authors have confirmed the association of tamoxifen use with development of endometrial polyps, EH, and abnormal vaginal bleeding [66]. Multiple studies have evaluated the EH and EC risk in tamoxifen treated breast cancer patients [66, 67]. In a randomized, double-blind trial, tamoxifen-treatment was shown to develop abnormal endometrial histology, proliferation, polyps, or mitotic cells in 39% of women, while 16% women showed atypical hyperplastic conditions [68]. Tamoxifen-treatment may result in endometrial thickness and polyps, leading to irregular endometrial linings that are associated with endometrial neoplasia [14, 69].

The development of EC due to tamoxifen is a leading cause of concern. One of the molecular theories being investigated is that tamoxifen-induced genotoxicity (e.g., induction of micronucleus formation and cytochrome P450s) causes unscheduled DNA-synthesis and mitotic-spindle disruption [70, 71]. The mechanism of tamoxifen action involves suppression of ER-dependent gene regulation in breast tissue and stimulation of ER-dependent gene regulation in the uterus [72, 73]. In endometrial cells, the tamoxifen-ERα complex is able to recruit co-activator proteins and initiate gene transcription, and this differential recruitment of a co-activator contributes to the tissue specificity of the function of the tamoxifen-ERα complex, which may ultimately result in EC [73, 74]. Tamoxifen was shown to up-regulate cancer markers in the endometrium, which are responsible for induction of EH and EC, such as ERα, progesterone receptor (PR), vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), mTOR, HER-2/neu, IGF-1R, and c-Myc [75, 76].

**Treatment options for endometrial hyperplasia**

Although there are no bonafide treatment procedures for EH, most current guidelines recommend hormone therapies (including use of progesterin, gonadotropin-releasing
hormone or its analogues or their combination) or surgical treatment (Figure-1). The selection criteria for treatment options are based on patient age, health, the presence of cytologic-atypia and fertility status (Figure-2). EH without-atypia responds well to progestins. Hormone therapy is also recommended for women whose general health prevents them from tolerating surgery due to coexisting medical conditions. However, women with atypical-EH or persistent EH without-atypia that are symptomatic (abnormal uterine bleeding) are treated with hysterectomy. Among women hoping for childbirth, EH treatment is challenging, demanding conservative treatment regardless of whether the hyperplasia is with or without-atypia.

**Progestin therapy**

Progestins, synthetic progestogens with similar effects as progesterone, are most frequently employed to induce-EH regression in women with EH without-atypia or those who wish to retain fertility. Progestins can provide hormonal contraception (either alone or with estrogen), and prevent EH development associated with unopposed estrogen. In addition, progestins have been found to decrease glandular cellularity by inducing apoptosis [77] and to inhibit angiogenesis in the myometrium immediately underlying the complex-EH [78]. Progestins can be given to patients via oral, intramuscular, micronized vaginal cream or intrauterine devices [16, 79]. This treatment has been highly successful in reversing EH with or without-atypia in patients on estrogen-alone replacement therapy [80], and was found to reduce EH in 61% of patients with atypical hyperplasia [5].

The mode and duration of progestin treatment is essential to its success. EH usually show a response after 10-weeks of dosing, but significant responses are commonly observed after 3-months of progestin therapy [81, 82], with the median time to resolution being 6-months [83]. Progestin therapy may be continued or hysterectomy performed in cases of
no response. Different types of progestins and their doses in clinical use for the treatment of EH are shown in table-3 and table-4, respectively.

**Medroxyprogesterone acetate (MPA)**

MPA is a synthetic steroidal progestin (synthetic steroid hormone progesterone) that is usually used to treat cases with absent or irregular menstrual periods, or abnormal uterine bleeding. MPA prevents overgrowth in the uterus lining in postmenopausal women receiving estrogen hormone and decreases the risk of EH progression. Cyclic MPA has been shown to be a safer and more acceptable therapy than continuous MPA [84]. A multicenter trial by Ushijima (2007) showed 82% complete and 18% partial response rates in EH patients receiving an MPA regimen with a 25 to 73-month follow-up [85]. Another study reported 54.8% remission by MPA [86]. MPA is commonly administered at 10mg per day, orally and continuously for 6-weeks, or cyclically for 3-months (2-weeks of each month) [80]. In patients having only partial response, MPA may be continued for another 3-months orally at a dose of 10mg, four times per day.

**Megestrol Acetate (MA)**

MA is a steroidal progestin (specifically, 17-hydroxylated progesterone) with predominantly progestational and antigonadotropic effects that has been shown to have the potential to inhibit proliferation in the uterus and treat EH. MA at doses ranging from 160–320mg/d has been reported to be an effective method of treatment for endometrial pathologies without causing marked harmful effects on serum lipid profiles or glucose levels [87]. Other studies also reported complete remissions of hyperplasia in more than 90% of patients [87, 88]. A Phase-II trial study of 31 patients with atypical-EH and well-to moderately-differentiated endometrial carcinoma receiving MA at a dose of 80mg (2
tablets) orally at breakfast and dinner for at least 12-weeks showed a positive response within 4 weeks, which was confirmed by endometrial biopsy or D&C/hysteroscopy.

https://clinicaltrials.gov/ct2/show/record/NCT00483327

Levonorgestrel (LNG)

LNG is a second generation progestin (synthetic progestogen) commonly used as an active component in some hormonal contraceptives. The LNG impregnated intrauterine device (LNG-IUS) is currently a very common treatment option for EH. This device releases a constant amount of LNG inside the uterus and effectively opposes the estrogenic effect [89].

A multicenter randomized trial of 170 women with low- or medium-risk EH was recently conducted to investigate the safety and effectiveness of LNG-IUS, Mirena®). Women treated with the LNG-IUS showed histologically normal endometrium after 6-months of therapy for EH. Moreover, cyclical progestogens were found to be less effective than continuous oral therapy and LNG-IUS [90]. Perimenopausal women (n=59) with non-atypical-EH treated with LNG-IUS showed an 88.1% (56/59) success rate after 12-months of treatment [91]. A study in the United Kingdom showed histological regression in 90% of patients with EH (n = 105) after 2-years of LNG-IUD treatment [92]. Another study reported 100% remission of EH by intrauterine-LNG [86].

Norethindrone acetate or norethisterone acetate

Norethisterone (or norethindrone) is a synthetic, orally active steroidal progestin with antiandrogen and antiestrogen effects [93]. It is commonly used as oral contraceptive pills and to treat premenstrual syndrome, irregular intense bleeding, irregular and painful
periods, menopausal syndrome (in combination with estrogen), or to postpone a period [94].

Various studies have validated use of norethisterone as an agent to reduce the incidence of EH in postmenopausal women treated with estradiol [66, 95]. A phase-III double-blind, randomized, multi-center study of norethisterone in 662 post-menopausal women was conducted from 2007 to 2009. The results showed 56% improvement in menopausal symptoms (ClinicalTrials.gov identifier: NCT00522873 [96]). Several other clinical trials have investigated application of norethindrone with a combination of LNG-IUS (ClinicalTrials.gov Identifier: NCT01499602) or with genistein (ClinicalTrials.gov Identifier: NCT00453960), but no final results have been posted to date.

Although various studies and randomized trials have shown that progestin is a potent therapeutic option for EH, there are some common side effects including dizziness, headache, nausea, abdominal pain, uterine pain, delay of menstruation, heavy menstruation, uterine bleeding, fatigue, diarrhea, vomiting, and painful menstruation. However, these symptoms commonly disappeared within 48-hours. Further, although the progestins have been widely used as nonsurgical management of EH, about 12-53% resistance rates were reported after progestin therapy [97]. Failure of progestin treatment may depend on various details such as a patient’s age, health, other diseases and, hyperplasia grade or type. Resistance may be due to inadequate/low level of progestin receptors, particularly PR-B, before treatment or alterations in PR regulatory function, co-activors and co-repressors [98]. Other molecular mechanisms for progestin resistance are dysregulation of TGF-α and EGFR in endometrial glandular cells, Fas/FasL and survivin expression, as well as insulin resistance [99, 100]. Hence, precautions such as routine checkups and biopsies are recommended for patients while on progestin therapy.
Therapies other than progestins

Danazol

Danazol, a synthetic androgen, is a derivative of 17α-ethinyltestosterone that is usually used as a treatment option for endometriosis [101]. Danzol can induce a hypo-estrogenic, as well as, a hypo-androgenic state in the uterus, resulting in atrophy of the endometrium [102, 103]. Various studies have shown the significant effects of danazol against EH [104-108]. Moreover, it has been suggested as an effective and safe alternative to progesterone for treatment of EH [106]. Danazol containing intrauterine devices (D-IUDs) might also be a novel and effective method for the treatment of EH [109]. However, some studies have suggested that danazol can increase the risk of ovarian cancer among women with endometriosis [110]. Other side effects of danazol include weight gain, muscle cramps, acne, seborrhea, decreased breast size, hirsutism, and deepening of the voice, which are all strongly related to androgenic action [111].

Genistein

Genistein is an isoflavonoid extracted from soy products that is a well-known inhibitor of protein-tyrosine kinases and topoisomerase-II [112, 113]. Genistein has been shown to suppress estrogen-induced genes such as c-fos and c-jun, as well as the internal cytokines IL-1α and TNF-α through cytokine- and estrogen receptor-mediated pathways [114]. Treatment with genistein aglycone (54 mg/day, n=19) for 6-months caused a 42% positive response rate in premenopausal women with non-atypical-EH [115]. A randomized double-blind, placebo and progesterone-controlled clinical trial also showed that after 6-months, 42% of genistein aglycone treated subjects showed significant improvement of symptoms, significantly reduced staining for ER-α and PR, and enhanced ER-β1 staining.
with complete regression of bleeding [116]. In a phase-II clinical trial (January 2007 - December 2008), genistein (54 mg/day daily for 6 months) was administered as a dietary supplement with norethisterone acetate and patients were found to recover from EH (ClinicalTrials.gov identifier: NCT00453960). These results prompted use of genistein aglycone for EH management, particularly in patient’s without-atypia. However, more studies and clinical trials are needed to establish genistein as a potent drug for the treatment of EH.

**Metformin**

Metformin (N,N-dimethylbiguanide) belonging to a class biguanides is commonly used for the treatment of type-2 diabetes mellitus [117] and PCOS, especially in over-weight and obese individuals [118], or in cases when insulin resistance may be an important factor [119]. Since insulin resistance is associated with the occurrence of atypical-EH [120] and metformin was shown to have anti-proliferative, anti-invasive, and anti-metastatic effects in multiple cancers, use of metformin is a logical approach for the treatment of EH [119-124]. Interestingly, metformin was shown to induce PR expression in EC cells [125], which may enhance progestin therapy efficiency or overcome the progestin resistance caused by PR depletion in long term progestin therapy.

Evrim et al. (2009) demonstrated the anti-proliferative effects of metformin on the endometrium in estradiol- or tamoxifen- treated mice [126]. Several studies have established metformin as an effective anti-estrogenic agent in the control of abnormal endometrial proliferative disorders or atypical-EH [119, 120, 127]. Tas (2013) verified that, similar to progesterone, metformin attenuates estrogen-induced EH in oopherectomized rats [128]. Metformin is now being studied in multiple cancer clinical trials (ClinicalTrials.gov identifier: NCT01685762), as well as in combination with LNG-IUS
Gonadotropin-releasing hormone (GnRH) therapy

The endometrium contains GnRH receptors and GnRH-agonists can down-regulate GnRH receptors upon prolonged exposure. GnRH analogues suppress the hypothalamic pituitary-ovarian axis, thereby inhibiting estrogen production. Thus, GnRH analogues appear to have a direct anti-proliferative effect on endometrial cells [130]. This has led to exciting and promising new avenues for EH therapy [131]. GnRH has been applied at a dose of 1 ampule/3.75 mg intramuscularly every 28 days for 6 months to treat women with EH, with or without-atypia. However, 25% of patients showed hyperplasia recurrence within 16-months of the completion of therapy [131]. A study, in which GnRH and tibolone (a synthetic steroid with both estrogenic and progestagenic effects) were used to treat EH, achieved complete remission in all patients, but with 19% recurrence within 2-years after cessation of therapy [132]. Accordingly, further study is needed to determine the usefulness of GnRH analogues before it can be recommended for clinical use in patients with atypical hyperplasia [133]. Different types of GnRH and its analogues evaluated for treatment of EH are shown in Table 3.

Various clinical trials for treatment of EH are summarized in table-5.

Surgical modalities

Since EH can progress to endometrial carcinoma, surgery is favored in most women with complex EH with-atypia if they have completed childbearing, do not desire preservation of their fertility or did not respond to hormone therapy [134]. Several surgical options have been widely reported as common treatments of atypical EH, such as thermal balloon
ablation, laser therapy or resectoscopic surgery. Thermal balloon endometrial ablation or resectoscopic endometrial ablation therapy is a feasible, safe, and effective treatment option for simple and complex non-atypical EH [135]; however, hysterectomy might be considered a first-choice treatment for EH [136, 137]. Resectoscopic surgery is an effective treatment for EH without-atypia, especially for those at high risk for medical therapy or hysterectomy [138]. It is also recommended that postmenopausal women with atypical EH undergo hysterectomy with concomitant bilateral salpingo-oophorectomy (BSO) rather than hysterectomy alone [139].

Women who undergo hysterectomies are at higher risk of developing stress incontinence. Although surgical modulations are well developed, studies with larger numbers of participants are still required to define their safety and efficiency before they can be recommended for all EH patients.

Limitations of existing therapies, need for further research, and future prospects for drug development

Currently, the recommended treatment approach for EH includes; cyclic progestin therapy, GnRH therapy and hysterectomy. The main limitations of the surgical methods (hysterectomy, hysteroscopic endometrial resection/ablation) are that they lead to the removal or disruption of the endometrium and can cause infertility and significant side effects. Progestins continue to be an effective option, especially for patients with low-grade ER and/or PR positive disease, some of whom achieve prolonged remission [140, 141]. Regrettably, progestin treatment contributes to reduction of PRs thereby causing response failure in adjuvant settings [140, 142, 143]. The disadvantages of GnRH therapy includes high cost, menopausal symptoms and bone demineralization associated with prolonged therapy [144]. Moreover, pre-operative use of GnRH has been accounted as a
risk factor for recurrence of fibroids. Hence, further research to identify new compounds and treatment strategies for this disease are warranted.

EH is a complex disease that may require simultaneously attacking more than one target or a systems approach for effective treatment. With the increased understanding of the molecular basis and the pathways related to particular disease progression, the era of molecularly targeted therapies has emerged as a most promising direction of research. For the development of personalized therapy agents in EH, pathways relevant to EH and EC may be targeted necessitating the careful research on molecular modulations in EH and endometrial tumors. Since EH is basically a hormone-dependent problem having high ER and/or PR expression, targeting ER may be a viable approach toward the development of novel treatment strategies for such disease.

Towards such an approach, pure antiestrogens represent endocrine-targeted therapy whose mechanism of action involves competition with the ER legands and ER down regulation. Fulvestrant (ICI 182,780) is used to treat hormone receptor-positive metastatic breast cancer in postmenopausal women by enhancing ER degradation [145]. Acolbifene (EM-652) and EM-800, are non-steroidal anti-estrogens that have been found to reduce uterine weight and uterine/vaginal ER expression [146]. In-vivo, acolbifene was devoid of any agonist activity in an immature rat uterotrophic assay and in mouse endometrial tissues [147, 148]. Additionally, acolbifene was more effective than Fulvestrant in inhibiting estradiol-induced EC and cell proliferation [149-151]. Taken together, these findings suggest that these antiestrogens may be beneficial to treat EH by reducing ER expression and acting as anti-proliferative agents.

The 2-[piperidinoethoxyphenyl]-3-[4-hydroxyphenyl]-2H-benzo(b) pyran, identified as an anti-estrogenic agent, is a non-steroidal, triarylethylene and triarylpropenone compound
which was found to inhibit uterine growth [140, 152-154]. The ability of this compound to inhibit uterine growth is attributed to its ability to antagonize estrogen action and apoptosis-inducing activities [154]. The activity of this compound has also been validated in primary cell culture of human atypical EH cells suggesting its potential use as a new targeted therapy for EH via inhibition of Wnt signaling, as well as inhibition of cell survival pathway [155].

Apart from the ovaries, fat tissues are the most common site for conversion of androgen to estrogen [156]. This locally produced estrogen results from over-expression of P450 aromatase in endometriotic tissue and increases the risk of endometrial hyperproliferation, EH and EC [157]. Aromatase inhibitors can inhibit estrogen production and thus reduce estrogen levels [158]. Examples of aromatase inhibitors include letrozole (Femara®), anastrozole (Arimidex®), and exemestane (Aromasin®), which are commonly used to treat breast cancer, and also thought to be helpful in the treatment of EC [159, 160]. Anastrozole or letrozole were shown to reduce endometrial thickness in patients with EH [161]. Recent studies have established Letrozole as good therapeutic option for simple EH without-atypia [162, 163]. Anastrozole was also found to be an interesting new modality for the treatment of EH in obese postmenopausal women [164]. Side effects of aromatase inhibitor treatment may include joint and muscle pain as well as hot flashes, bones weakening and occasionally osteoporosis.

Further, although, tamoxifen is well known inducer of endometrial proliferation, it is a major therapeutic option for breast cancer, so we cannot ignore its importance as a potent therapeutic agent. Till now, various studies have been carried out to overcome the side effects of tamoxifen on the uterus [165-167]. Since, tissue specific actions of SERMs are based on various molecular components in specific cellular environments including the
ERα to ERβ ratio and of co-activators and co-repressors [168], an approach to modulate tissue specific tamoxifen action in the uterus could also be a fascinating area of research involving development of new drugs that prevent the uterine estrogenic activity in a combination therapy with tamoxifen in breast cancer treatment. Combination with progestin or cyclic therapy of tamoxifen for breast cancer treatment needs more attention to prevent tamoxifen induced hyperplasia of endometrium.

Therapies targeted at immune cytokines that are elevated in EH and EC are also a promising avenue of investigation. A neutralizing antibody to human IL-22, was shown to inhibit proliferation of EC cells [169]. Multiple neutralizing antibodies and small chemical inhibitors of IGF-R1 are being studied in EC and could have applicability to treat EH if their toxicity profiles prove acceptability for a cancer prevention application [46]. Similarly, a CCL2 neutralizing antibody and a CCR2 antagonist, which have been shown to inhibit endometrial stromal cell proliferation could potentially be studied for treatment of EH given appropriate safety profiles [170]. There are a wide variety of pharmaceuticals in clinical use and trial for treatment of a variety of diseases including cancer, which also might have applicability for targeting the imbalance of cytokines involved in the development of EH and progression to cancer.

**Summary:**

EH being a precursor of EC is of clinical importance. Available therapeutic options for EH, such as progestin, danazol, genistein, metformin and GnRH therapy or surgery have restricted efficiency due to high cost, side effects and drug resistance. Further, EH treatment is still challenging in patients whose wish to retain their fertility. As a novel approach, the antiestrogens, aromatase inhibitors and cytokines might give optimistic outcomes for EH, however; clinical trials are needed to prove their efficacy. Various
mutations and SNP in pathobiology of EH should be also targeted to achieve better therapeutic response. Future investigations and clinical trials with these novel compounds in combination with known established EH therapies are required to achieve precise management of EH. Further research on the cellular signaling pathways that control endometrial cell proliferation and development of EH, as well as targeting various mutations and SNP in pathobiology of EH will help to identify novel targeted therapeutic agents to improve the management of EH.
CONFLICT OF INTEREST

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


40


**Figure Legend**

**Figure 1.** Overview of endometrial hyperplasia, risk factors, classification and treatment options. **A)** The cross-sectional view of uterus showing endometrium. **B)** HE staining of endometrium at proliferative and secretory phase of endometrium*. **C)** Risk factors associated with endometrial hyperplasia. **D)** The cross-sectional view of uterus showing proliferative endometrium and the HE staining of endometrium hyperplasia showing abnormal increase of endometrial glands. **E)** HE stained section of endometrial, (a) Proliferative endometrium, (b) Simple hyperplasia, (c) Complex hyperplasia and (d) Complex atypical hyperplasia**. **(F)** Different therapeutic options of endometrial hyperplasia. * Fig. taken from Horne and Blithe (2007) [3]; ** Fig. taken from Palmer et al., 2008 [15].
Figure 2. The investigations and management schemes for endometrial hyperplasia.
<table>
<thead>
<tr>
<th>Classifying year</th>
<th>Classifying type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961</td>
<td>Benign hyperplasia</td>
<td>Atypical hyperplasia type I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical hyperplasia type II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical hyperplasia type III</td>
</tr>
<tr>
<td>1963</td>
<td>Mild adenomatous hyperplasia</td>
<td>Moderate adenomatous hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked adenomatous hyperplasia</td>
</tr>
<tr>
<td>1966</td>
<td>Cystic hyperplasia</td>
<td>Adenomatous hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>1972</td>
<td>Cystic hyperplasia</td>
<td>Adenomatous hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>1978</td>
<td>Cystic hyperplasia</td>
<td>Adenomatous hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>1979</td>
<td>Hyperplasia without atypia</td>
<td>Hyperplasia with mild atypia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperplasia with severe atypia</td>
</tr>
<tr>
<td>1985</td>
<td>Simple, Nonatypical</td>
<td>Complex, Nonatypical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple atypical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complex atypical</td>
</tr>
<tr>
<td>WHO (1994)</td>
<td>Simple hyperplasia</td>
<td>Complex hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple hyperplasia with atypia</td>
</tr>
<tr>
<td>WHO (2003) (Revised)</td>
<td>Proliferative endometrium-</td>
<td>Simple hyperplasia-</td>
</tr>
<tr>
<td></td>
<td>Tubular and regularly spaced gland</td>
<td>Irregular shape and size glands</td>
</tr>
<tr>
<td></td>
<td>Glands are lined with pseudostratified nuclei</td>
<td>Cystic appearance</td>
</tr>
<tr>
<td></td>
<td>Abundant stroma</td>
<td>abundant stroma,</td>
</tr>
<tr>
<td></td>
<td>Mitotic figures are easily found both in glands and stroma</td>
<td>No back to back crowding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nuclear pseudostratified glands but no nuclear atypia</td>
</tr>
<tr>
<td></td>
<td>Complex hyperplasia-</td>
<td>Closely packed glands</td>
</tr>
<tr>
<td></td>
<td>Tubular and regularly spaced gland</td>
<td>Struma is relatively sparse</td>
</tr>
<tr>
<td></td>
<td>Glands are lined with pseudostratified nuclei</td>
<td>Gland to stroma ratio is more than 2:1</td>
</tr>
<tr>
<td></td>
<td>Abundant stroma</td>
<td>Nuclei are uniform, oval and pseudostratified</td>
</tr>
<tr>
<td></td>
<td>Mitotic figures are easily found both in glands and stroma</td>
<td>Nucleoli are indistinct</td>
</tr>
<tr>
<td></td>
<td>Complex atypical hyperplasia-</td>
<td>Tightly packed glands</td>
</tr>
<tr>
<td></td>
<td>Tubular and regularly spaced gland</td>
<td>Very little intervening stroma</td>
</tr>
<tr>
<td></td>
<td>Glands are lined with pseudostratified nuclei</td>
<td>Larger and vascular nuclei with chromatin clumped along the nuclear membrane</td>
</tr>
<tr>
<td></td>
<td>Abundant stroma</td>
<td>Prominent nucleoli</td>
</tr>
<tr>
<td></td>
<td>Mitotic figures are easily found both in glands and stroma</td>
<td></td>
</tr>
<tr>
<td>EIN</td>
<td>Benign or endometrial hyperplasia</td>
<td>EIN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma</td>
</tr>
</tbody>
</table>
EIN, Endometrial intraepithelial neoplasia [178].
Table 2. Risk factors for endometrial hyperplasia

<table>
<thead>
<tr>
<th>Risk factors category</th>
<th>Factors inducing EH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual and Parity status</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td></td>
<td>Null parity</td>
</tr>
<tr>
<td></td>
<td>Late menopause or Early menarche</td>
</tr>
<tr>
<td></td>
<td>Chronic anovulation</td>
</tr>
<tr>
<td>Pre-existing Disease</td>
<td>Obesity/ Overweight/High BMI</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovarian syndrome</td>
</tr>
<tr>
<td></td>
<td>Androgen-secreting tumors</td>
</tr>
<tr>
<td></td>
<td>Hereditary non-polyposis colonic cancer (Lynch-syndrome)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>Prolonged exogenous estrogen exposure</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Estrogen replacement therapy</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>SNPs (CYP2D6, CYP17, COMT, APOE and HFE)</td>
</tr>
<tr>
<td></td>
<td>PTEN, K-ras, β-catenin, PIK3CA mutations</td>
</tr>
<tr>
<td></td>
<td>Deletions on the short arm of chr-8</td>
</tr>
<tr>
<td></td>
<td>MSI</td>
</tr>
<tr>
<td>Inflammatory markers and Cytokines</td>
<td>TNF-α, PCNA, EGF, Fas., TNF-R1, IGF-1, NF-κB, IL-22</td>
</tr>
</tbody>
</table>

*Single nucleotide polymorphism (SNP), Cytochrome P450 2D6 (CYP2D6), Cytochrome P450 17A1 (CYP17), Catechol-O-methyltransferase (COMT), Apolipoprotein E (APOE), and Hemochromatosis (HFE), Phosphatase and tensin homolog (PTEN), Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA), Chromosome (Chr), Microsatellite instability (MSI), Tumor necrosis factor-α (TNF-α), Proliferating cell nuclear antigen (PCNA), Epithelial growth factor (EGF), Tumor necrosis factor receptor 1 (TNF-R1), Insulin-like growth factor 1 receptor (IGF-1R) and V-myc avian myelocytomatosis viral oncogene homolog (c-MYC), Insulin-like growth factor-1 (IGF-1), Nuclear factor-κB (NF-κB), Interleukin-1β (IL-1β).*
Table 3: Common therapies for endometrial hyperplasia

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Origin and formula</th>
<th>Routes of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progestin therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxy progesterone acetate</td>
<td>Steroidal progestin (C_{24}H_{34}O_{4})</td>
<td>Oral; intramuscular</td>
</tr>
<tr>
<td>Megestrol Acetate</td>
<td>Steroidal progestin (C_{24}H_{32}O_{4})</td>
<td>Oral</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Synthetic progestogen (C_{21}H_{28}O_{2})</td>
<td>Implant; insert (extended-release); oral</td>
</tr>
<tr>
<td>Norethisterone acetate</td>
<td>Steroidal progestin (C_{22}H_{28}O_{3})</td>
<td>Oral</td>
</tr>
<tr>
<td>Megestrol Acetate + Metformin</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Levonorgestrel-IUD + Metformin</td>
<td></td>
<td>Oral or implant; insert (extended-release)</td>
</tr>
<tr>
<td><strong>Other than progestin therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td>Synthetic steroid ethisterone (C_{22}H_{27}NO_{2})</td>
<td>Oral</td>
</tr>
<tr>
<td>Genistein</td>
<td>Isoflavones (C_{15}H_{10}O_{3})</td>
<td>Oral</td>
</tr>
<tr>
<td>Metformin</td>
<td>Biguanide class (C_{6}H_{11}N_{5})</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>GnRH Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histrelin</td>
<td>D-His(B21)6, Pro9-Net-GnRH (C_{66}H_{86}N_{18}O_{12})</td>
<td>Subcutaneous implant</td>
</tr>
<tr>
<td>Nafarelin</td>
<td>D-Nal(2)6-GnRH (C_{66}H_{83}N_{17}O_{13})</td>
<td>Nasal spray</td>
</tr>
</tbody>
</table>

(Glu-Glutamic acid, His-Histidine, Trp-Tryptophan, Ser-Serine, Tyr-Tyrosine, Gly-Glycine, Leu-Leucine, Arg-Arginine, Pro-Proline. NH_{2}-Amino group.)
Table 4: Common doses of various progestins for treatment of endometrial hyperplasia

<table>
<thead>
<tr>
<th>Progestin type</th>
<th>Common name</th>
<th>Common doses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometrial type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benign or simple hyperplasia</strong></td>
<td>Progesterone, Progestasert, Crinone, Endometrin</td>
<td>300 mg PO × 14days /months</td>
<td>[79, 178]</td>
</tr>
<tr>
<td><strong>Atypical hyperplasia or EIN</strong></td>
<td></td>
<td>300 mg/day PO</td>
<td></td>
</tr>
<tr>
<td><strong>Medroxy Progesteron acetate</strong></td>
<td>Depo-provera (injection), Provera (oral)</td>
<td>10 mg PO × 14days /months</td>
<td></td>
</tr>
<tr>
<td><strong>Megestrol acetate</strong></td>
<td>Megace</td>
<td>80 mg PO × 14days /months</td>
<td></td>
</tr>
<tr>
<td><strong>Levonorgestrol-IUD</strong></td>
<td>Mirena, Orplant</td>
<td>20 µg/days × 6 months to 2 years</td>
<td></td>
</tr>
</tbody>
</table>

IM, intramuscularly; PO, orally; LNG, levonorgestrol; IUD, intra-uterine device; EIN, endometrial intraepithelial neoplasia.
Table 5: Clinical trials for endometrial hyperplasia

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier (Study type)</th>
<th>Hyperplasia grade</th>
<th>Drugs</th>
<th>No of patients (age range)</th>
<th>Phase trial</th>
<th>Study Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01499602 (Interventional)</td>
<td>Simple or complex EH without atypia</td>
<td>Levonorgestrel and Norethisterone Acetate</td>
<td>120 (40-50 yrs)</td>
<td>May 2009-Nov 2011</td>
<td>Achieve complete regression</td>
<td></td>
</tr>
<tr>
<td>NCT00453960 (Interventional)</td>
<td>Non atypical EH</td>
<td>Genistein and Norethisterone Acetate</td>
<td>59</td>
<td>II</td>
<td>Jan 2007-Nov 2008</td>
<td>Recovery from endometrial hyperplasia</td>
</tr>
<tr>
<td>NCT01234818 (Interventional)</td>
<td>EH</td>
<td>LNG-IUS</td>
<td>80</td>
<td>II</td>
<td>Nov 2010-Nov 2012</td>
<td>Endometrial aspiration biopsy shows exacerbation, treatment with LNG-IUS must be stopped and other specific treatment should be initiated.</td>
</tr>
<tr>
<td>NCT01685762 (Interventional)</td>
<td>Asymptomatic EH</td>
<td>Metformin</td>
<td>~15 (18-75yrs)</td>
<td>0</td>
<td>Jul 2012-Apr 2014</td>
<td>No study results posted on clinicaltrials.gov yet</td>
</tr>
<tr>
<td>NCT01074892 (Interventional)</td>
<td>EH</td>
<td>MPA and Levonorgestrel</td>
<td>170 (30-70yrs)</td>
<td>IV</td>
<td>May 2005-May 2012</td>
<td>Regression of hyperplasia after 6 months of therapy but recurrence and Side effects during 2 year follow-up treatment</td>
</tr>
<tr>
<td>NCT00483327 (Interventional)</td>
<td>Atypical EH</td>
<td>Megestrol Acetate</td>
<td>31 (&gt;18yrs)</td>
<td>II</td>
<td>Jun 2007-Nov 2013</td>
<td>Best pathologic response rates</td>
</tr>
<tr>
<td>NCT01686126 (Interventional)</td>
<td>Complex atypia EH</td>
<td>Levonorgestrel and Metformin</td>
<td>165 (&gt;18yrs)</td>
<td>II</td>
<td>Sep 2012-Dec 2014</td>
<td>Pathological complete response</td>
</tr>
<tr>
<td>NCT00490087 (Interventional)</td>
<td>Atypical endometrial polyps and atypical EH</td>
<td>LNG-IUD</td>
<td>21 (25-50yrs)</td>
<td>III</td>
<td>Jun 2007-Sep 2011</td>
<td>Recurrence of polyp in the two groups</td>
</tr>
<tr>
<td>NCT ID</td>
<td>Type</td>
<td>Condition</td>
<td>Participant Age</td>
<td>Intervention Duration</td>
<td>Main Outcome</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>NCT00883662</td>
<td>Observational</td>
<td>EH Levonorgestrel</td>
<td>2680 (&gt;18yrs)</td>
<td>Jun 2009-Apr 2015</td>
<td>Patient distribution per indication</td>
<td></td>
</tr>
<tr>
<td>NCT00919919</td>
<td>Interventional</td>
<td>EH and EC progesterone</td>
<td>60 (45-60yrs)</td>
<td>II Jun 2009-Nov 2010</td>
<td>Comparing the proportion of women with endometrial thickness not exceeding 8mm and change not exceeding 3mm between the two groups.</td>
<td></td>
</tr>
<tr>
<td>NCT01968317</td>
<td>Interventional</td>
<td>Atypical EH Megestrol Acetate and Metformin</td>
<td>~150 (18-45yrs)</td>
<td>II Oct 2013-Apr 2015</td>
<td>Got Pathological response rate</td>
<td></td>
</tr>
<tr>
<td>NCT00788671</td>
<td>Interventional</td>
<td>Complex atypical EH LNG-IUD</td>
<td>~50 (&gt;18yrs)</td>
<td>II Nov 2008-Mar 2015</td>
<td>Complete Regression of Disease</td>
<td></td>
</tr>
<tr>
<td>NCT02035787</td>
<td>Interventional</td>
<td>Complex atypical EH LNG-IUD Metformin</td>
<td>~30 (&gt;18yrs)</td>
<td>- Jan 2014-Jul 2014</td>
<td>Percent of individuals achieving complete disease regression as defined by no evidence of microscopic viable hyperplasia or carcinoma on endometrial biopsy after 6 months of treatment compared to a base rate of 50%</td>
<td></td>
</tr>
</tbody>
</table>

Yrs: Years; EH: Endometrial hyperplasia; EC: Endometrial cancer; MPA: Medroxy-progesterone acetate; LNG-IUD: levonorgestrel-impregnated intrauterine device.