International Journal of Research and Review
Vol. 10; Issue: 3; March 2023
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Endometrial Hyperplasia as an Endometrial Cancer Risk Factor: Review Article

Ervina Pratiwi

Tiom Regional General Hospital, Lanny Jaya Regency, Tiom-Papua, Indonesia
Faculty of Medicine, University of HKBP Nommensen Medan-Indonesia

DOI: https://doi.org/10.52403/ijrr.20230333

ABSTRACT

The most prevalent cancer of the female reproductive tract in developed nations is Endometrial carcinoma (EC), preceded by endometrial hyperplasia (EH). EH is a non-invasive, abnormal growth of the uterine endometrial lining that carries a high risk of developing into EC or progressing to it. Premenopausal women's bleeding problems and postmenopausal women's vaginal bleeding are EH's main signs and symptoms. Chronic exposure to unopposed estrogen is the leading risk factor for the development of EH. Clinical management can range from monitoring to progestin therapy to a hysterectomy, depending on the risk of EC progression or concomitant EC and the patient's desire to maintain fertility. According to several studies, progestins effectively treat both benign and atypical EH. Endometrial cancer is relatively understudied compared to other malignancies with greater public awareness, such as ovarian and cervical. Therefore, in this review, we discuss Endometrial Hyperplasia as a risk factor an Endometrial Cancer

Keywords: Endometrial hyperplasia, Endometrial cancer, Progestins effectively

INTRODUCTION

Endometrial hyperplasia is characterized by an abnormal rise in the ratio of the endometrial glands to the stroma compared to proliferative endometrium. In the West, endometrial cancer is the most prevalent gynecological disease. The incidence of endometrial cancer is expected to reach pandemic levels in the following decades due to an increase in the rate of obesity, and endometrial hyperplasia is the condition that precedes it. Endometrial hyperplasia is thought to occur at least three times more frequently than endometrial cancer, and if ignored, it can develop into cancer. Endometrial hyperplasia most often manifests as irregular uterine bleeding. This includes postmenopausal, heavy menstrual, intermenstrual, and unscheduled bleeding while taking hormone replacement treatments. [(1),(2)] According to histopathology, EH may be divided into benign EH (without atypia) and atypical EH/endometrial intraepithelial neoplasia (EIN). Chronic exposure to unopposed estrogen is the most critical risk factor. [(1)]

DIAGNOSIS AND SCREENING

Even though up to 80% of women who appear with atypical bleeding do not have endometrial cancer, an invasive test is still performed on them. In women who experience abnormal bleeding, an endometrial thickness of 4 millimeters on transvaginal ultrasound can reduce their chance of bleeding. The chance of endometrial cancer to less than 1%, yet this threshold has a high prevalence of false positives and poor sensitivity in asymptomatic women. [(3),(4)] Inconvenience, bleeding, infection, and uterine perforation can occur due to endometrial samples for diagnostic purposes. Biopsies may not be enough in as many as 25% of instances. There is no screening procedure for endometrial cancer for the general populace.

From age 35, women with Lynch syndrome and their first-degree relatives are given yearly screenings with ultrasound and endometrial biopsies. However, no evidence exists that these procedures lead to an earlier discovery of endometrial cancer. A 40–60% lifetime risk exists for endometrial cancer in those with Lynch syndrome. [(5)] If abnormal bleeding continues or intrauterine structural abnormalities, such as polyps, are detected on TVS or endometrial biopsy, hysteroscopy with extra endometrial assessment may be required. Hysteroscopy can help or supplement endometrial biopsies, particularly in cases where sampling is not feasible or non-diagnostic. A systematic quantitative evaluation of data from 26 346 women was conducted to assess the efficacy of hysteroscopy in the diagnosis of cancer and hyperplasia in women with abnormal bleeding. From a pretest probability of 3.9%, a positive hysteroscopy result (positive LR 60.9) raised the likelihood of cancer to 71.8%, whereas a negative hysteroscopy result (negative LR 0.15) decreased the likelihood of cancer to 0.6%. Whereas Hyperplasia is not frequently diagnosed using CT or MRI. According to a preoperative CT scan study, treating women with grade 1 endometrial cancer or atypical endometrial hyperplasia may change in 4.3% of cases. However, no studies examine its use for monitoring women receiving conservative treatment for endometrial hyperplasia. [(1),(4)]

ENDOMETRIAL HYPERPLASIA CLASSIFICATION AND RISK OF DEVELOPING INTO ENDOMETRIAL CARCINOMA

Endometrial hyperplasia is the histological term for the aberrant proliferation of endometrial glands with a more excellent gland-to-stroma ratio than healthy proliferative endometrium and without endometrial stromal invasion. A tissue sample obtained from an endometrial biopsy, curettage, or hysterectomy should be the foundation for the diagnosis. The 2014 World Health Organization (WHO) Categorization System makes the following distinctions. It is the most often used classification scheme for EH—endometrial intraepithelial neoplasia (atypical EH) and benign endometrial hyperplasia (benign EH) (EIN). [(1),(6)]

This distinction is crucial since the clinical therapy of the two disorders differs depending on whether nuclear atypia is present or not. Enlargement of the nucleus with or without prominent nucleoli is called atomic atypia. EH without atypia is a benign lesion without significant somatic genetic alterations brought on by prolonged estrogen exposure and not mitigated by progestin-protective actions. The hyperplastic alterations retreat, and the endometrium often return to normal when physiological progesterone levels are restored, or therapeutic progestins are taken. Although the evidence for this claim is weak, it appears that EH without atypia rarely progresses to EC. For instance, just two (1.6%) of 122 patients with benign EH advanced to EC in a case series published in 1985. Eleven years after the initial diagnosis of simple hyperplasia, the first patient experienced atypical EH and later EC. After being diagnosed with complex EH, the second patient eventually developed EC 8.3 years later. Neither of the patients had undergone progestin therapy or passed away from their illness. [(2),(4)]

RISK FACTORS OF ENDOMETRIAL HYPERPLASIA

Multiple observable risk factors are frequently linked to endometrial hyperplasia, so assessment should focus on locating and tracking these variables. Endometrial hyperplasia occurs when estrogen stimulates endometrial cell growth by binding to estrogen receptors in the

nuclei of endometrial cells without being inhibited by progesterone. Increased body mass index (BMI) with excessive peripheral androgen to estrogen conversion in adipose tissue, anovulation related to perimenopause or polycystic ovary syndrome (PCOS), estrogen-secreting ovarian tumors, such as granulosa cell tumors (with an endometrial hyperplasia prevalence of up to 40%), and drug-induced endometrial stimulation, such as the use of systemic estrogen replacement, are known risk factors Unopposed estrogen replacement treatment, according to a Cochrane meta-analysis, is not advised for use in women who have uteruses because it raises the risk of hyperplasia at all doses. Immunosuppression and infection may also play a role in the development of the disease, even though estrogenic stimulation of the endometrium is thought to be the primary aetiological risk factor. [(1),(4)]

EXPOSURE TO ENDOGENOUS ESTROGEN

Obesity, persistent anovulation, early menarche, late menopause, and the presence of estrogen-secreting tumors are a few examples of high endogenous estrogen exposure. Adipose tissue mass is inversely correlated with circulating and local estradiol levels in obese women. Numerous mechanisms can be used to explain this. First, an increase in the secretory activity of the adrenal glands, which raises androgen precursor levels, is frequently observed. These precursors may then undergo estradiol synthesis in peripheral organs.[(4),(7)] Furthermore, the enzyme aromatase converts androstenedione to estrone more quickly since it happens primarily in fat tissue. Not to mention, obese persons have higher amounts of estradiol because their plasma levels of the hormone-binding protein SHBG, which binds to estradiol, usually are lower. Chronic anovulation is an additional significant risk factor for EH. When anovulation occurs, unlike in premenopausal women who ovulate regularly, sex hormone production is not cyclical. Absent ovulation, progesterone released by the corpus luteum after ovulation has little effect. Therefore estrogen levels continue to be dominant. An increased risk of developing EH and, ultimately, endometrioid EC results from this imbalance, which causes the endometrium to continue to grow. Polycystic ovarian syndrome (PCOS), hyperprolactinemia, and hormonal status during perimenopause are frequently linked to anovulation.[(7),(8)]

EXPOSURE TO EXOGENOUS ESTROGEN

Estrogen therapy should always be combined with progestin in women with an intact uterus. Unopposed estrogen medication increases the likelihood of developing EH and later EC in premenopausal and postmenopausal women with intact uteruses. When women are treated with estrogen alone, the risk of EH becomes much higher. After 12 months of unopposed moderate or high-dose estrogen therapy and after 18 to 24 months of unopposed low-dose estrogen therapy, the risk rose. Tamoxifen has been linked to a higher risk of developing EH and EC and is one of the most effective drugs for the endocrine treatment of hormone receptor-positive breast cancer. Numerous modest investigations concluded that tamoxifen-related ECs are typically discovered early and have a generally positive outlook. [(9)] Endocrine therapy with tamoxifen, however, significantly outweighs the higher risk of EC in patients with hormone receptor-positive breast cancer in terms of advantages. On the other hand, the preventive use of tamoxifen in healthy patients must be critically examined in light of the available information. According to two studies, the increased risk of EH and EC in tamoxifen users may only apply to postmenopausal women. [(4),(9)]

ENDOMETRIAL HYPERPLASIA MANAGEMENT

When treating EH, a variety of various factors should be taken into account. The patient's medical history and histological characteristics should be used to ascertain any known risk factors for EC development or the concurrent existence of the disease. Given the diagnostic ambiguities in distinguishing between EH, atypical EH, and EC, a qualified gynecopathologist should also be contacted. To guarantee the comparability of histopathological data in clinical practice and academic research, the 2014 WHO classification of EH should be utilized for EH without atypia (benign EH) and atypical EH. The most crucial element in adequately planning and monitoring therapy is whether or not there is nuclear atypia. The leading cause of EH is prolonged exposure to unopposed estrogen. Therefore, removing the source of excessive estrogen in any form of treatment is essential. This can be done by helping obese people lose weight, halting unopposed estrogen therapy, treating anovulation, or locating and removing estrogen-secreting tumors. Depending on their family planning status, it's also critical to consider the need for contraception and fertility concerns in premenopausal EH patients. [(1),(4),(10)]

Surgical Treatment

Atypical EH carries a high risk of illness progression or concurrent EC. Therefore, most patients with atypical EH should receive hysterectomy recommendations, notably all postmenopausal patients and premenopausal women who have finished having children. Progestin therapy with close monitoring might be an alternative if surgery is not an option or the patient wants to protect her fertility. A total hysterectomy is the preferred curative procedure for people with atypical EH who are surgical candidates. A supracervical approach shouldn't be advised because precancerous lesions on the cervix may be present.[(10),(11)]

The uterine specimen might be examined grossly or freeze sectioned intraoperatively to check for malignant illness. However, the frozen section has a low sensitivity, only detecting EC at a rate of between 73% and 88% during surgery. Notably, one study even stated that the sensitivity was only 27%. Bilateral salpingo-oophorectomy must also be considered in women with early EC due to the high frequency of ovarian cancer in young women with EC. A comprehensive literature analysis revealed 2904 cases of women with EC and ovarian cancer (SEOC), 1035 of whom (36%) were premenopausal or under 50. There were 842/23,498 women with SEOC among all cases of EC that were recorded. Forty percent of the women tested had microsatellite instability and mutations in mismatch repair genes compatible with HNPCC. Therefore, synchronous ovarian cancer is quite likely in young women with EC. It is advised that young women with EC have bilateral salpingo-oophorectomy or a thorough histological examination of both ovaries to confirm or rule out SEOC. All young women with EC should be eligible to have HNPCC testing. Every patient should have a personal conversation about the possibility of bilateral salpingo-oophorectomy, taking into account any potential dangers of the different treatments, as well as long-term side effects and the risk of ovarian cancer.[(10),(11)]

Progestin Treatment

Numerous studies show that progestins are effective in treating benign and atypical EH. Therefore, progestin treatment is the most popular method for treating women with EH. The endometrial stroma becomes decidualized due to the progesterone supply activating progesterone receptors, which then causes endometrial thinning. Progestin administration ought to be the initial course of treatment, particularly in premenopausal women with mild EH who want to keep

their fertility. If a high risk of concurrent EC is identified, an initial endometrial biopsy must be followed by a dilation and curettage procedure to screen for malignancy. Patients with hormone receptor-positive breast cancer, thrombophilia, liver failure, and progestin allergies should not get progestin therapy during pregnancy.[(1),(12)]

It has been demonstrated that various progestins and administration methods help treat EH. In many nations, the levonorgestrel-releasing intrauterine device (LNG-IUD), which releases 20 g of LNG per 24 hours (LNG 52/5) for 4 to 5 years, has supplanted oral progestin therapies as the standard of treatment. Regression to healthy endometrium has been documented in up to 90% of women with benign EH following treatment with the LNG 52/5 IUD. Approximately 75–85 percent of patients with atypical EH and early EC with LNG 52/5 IUD treatment resulted in complete regression. Randomized trials revealed that the LNG 52/5 IUD, which has fewer systemic side effects and is an effective form of contraception, is more efficient than orally administered progestins in treating EH. The LNG 52/5 IUD avoids hepatic and intestinal flora metabolism, where progestin is linked to sedative effects by its local action on the endometrium. Oral progestins can cause bloating, nausea, headaches, mood fluctuations, and even melancholy. Another usual side effect of progestin therapy is irregular vaginal bleeding, including spotting. This holds for intrauterine and oral treatments alike.[(12),(13)]

The LNG 52/5 IUD may not be an acceptable therapeutic option for all patients with EH, although having a higher potential for effectiveness. When it comes to patients with dysmenorrhea brought on by IUDs, women eager to start a family, or when anatomical complications make IUD insertion difficult, oral progestins may be a preferable option. Patients should receive a steady therapeutic dose of oral progestins for three to six months to treat EH. Progestin monotherapies and medications combining estrogen and progestin are examples of treatments (oral contraceptives). Megestrol acetate and MPA are the most popular oral progestin nanotherapeutics, as was already mentioned. According to the type of EH, different MPA doses have been utilized in the literature, ranging from 10 mg for benign EH to 600 mg for severe EIN. Overall, progestin therapy should be continually taken at larger doses for treating EIN than for treating benign EH. Furthermore, cyclic progestin therapy is more commonly compared to the continuous quantity associated with irregular vaginal bleeding.[(13),(14)]

These drugs don't offer contraception, though. Premenopausal women utilizing these therapies should be encouraged to use supplementary birth control because progestin medicines are contraindicated during pregnancy. Although progesterone action is predominant at the tissue site in combined estrogen-progestin medications, no high-quality data currently supports oral contraceptives' use in treating EH. Endometrial samples should be done every three to six months to assess the effectiveness of progestin medication therapeutically. A comprehensive follow-up is required, particularly in women with atypical EH. To preserve fertility, premenopausal patients may stop taking progestin after three to six months and try to get pregnant if regression to a healthy endometrium can be shown histologically. Some EH patients can conceive after completing progestin medication. Progesterone therapy should be continued as maintenance therapy with additional follow-up via endometrial sampling in postmenopausal or premenopausal women who are not immediately interested in getting pregnant. This is especially

important if vaginal bleeding abnormalities repeat. Hysterectomy is advised if atypical EH persists or if EC manifests despite ongoing progestin medication.[14],[15]

CONCLUSION

Compared to proliferative endometrium, endometrial hyperplasia is characterized by an abnormal increase in the ratio of endometrial glands to the stroma. Endometrial cancer monitoring is not available to the general population. Endometrial tissue must be evaluated histologically to diagnose endometrial hyperplasia. Premenopausal and postmenopausal women may benefit from transvaginal ultrasound to diagnose endometrial hyperplasia. When endometrial hyperplasia is interpreted within a polyp or other discrete focal lesion, hysteroscopy should be used to visualize the uterine cavity and obtain a biopsied sample directly. Obesity and hormone replacement therapy (HRT) are reversible risk factors that should be identified and, if possible, addressed. Observation alone with follow-up endometrial biopsies to ensure disease regression is a viable option, particularly when identifiable risk factors can be reversed. Progestins are effective in treating benign and atypical EH. Therefore, progestin treatment is the most popular method for treating women with EH.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. RCOG/BSGE Joint Guideline. Management of Endometrial Hyperplasia.2016 February (67):1-30
2. Uterine cancer incidence statistics | Cancer Research UK [Internet]. [cited 2023 Feb 22]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence#heading-One
3. Seckin B, Cicek MN, Dikmen AU, Bostancı EI, Muftuoglu KH. Diagnostic value of sonography for detecting endometrial pathologies in postmenopausal women with and without bleeding: Sonography and endometrial pathologies. J Clin Ultrasound. 2016 Jul 8;44(6):339–46.
4. Nees LK, Heublein S, Steinmacher S, Juhasz-Böss I, Brucker S, Tempfer CB, et al. Endometrial hyperplasia as a risk factor of endometrial cancer. Arch Gynecol Obstet. 2022 Jan 10;306(2):407–21.
5. Hutt S, Tailor A, Ellis P, Michael A, Butler-Manuel S, Chatterjee J. The role of biomarkers in endometrial cancer and hyperplasia: a literature review. Acta Oncol. 2019 Mar 4;58(3):342–52.
6. Kurman R, Carcangiu M, Herrington C, Young R. WHO Classification of Tumours of Female Reproductive Organs. 4th Edition. 2014. (IARC; vol. Volume 6).
7. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014 Sep 1;20(5):748–58.
8. Rosen MW, Tasset J, Kobernik EK, Smith YR, Johnston C, Quint EH. Risk Factors for Endometrial Cancer or Hyperplasia in Adolescents and Women 25 Years Old or Younger. J Pediatr Adolesc Gynecol. 2019 Oct;32(5):546–9.
9. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Gynaecology and Fertility Group, editor. Cochrane Database Syst Rev [Internet]. 2012 Aug 15 [cited 2023 Feb 22]; Available from: https://doi.wiley.com/10.1002/14651858.CD000402.pub4
10. Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of Endometrial Precancers: Obstet Gynecol. 2012 Nov;120(5):1160–75.
11. Morotti M, Menada MV, Moioli M, Sala P, Maffeo I, Abete L, et al. Frozen section pathology at time of hysterectomy accurately predicts endometrial cancer in patients with preoperative diagnosis of

atypical endometrial hyperplasia. Gynecol Oncol. 2012 Jun;125(3):536–40.
12. Wong AWY, Chan SSC, Yeo W, Yu MY, Tam WH. Prophylactic Use of Levonorgestrel-Releasing Intrauterine System in Women With Breast Cancer Treated With Tamoxifen: A Randomized Controlled Trial. Obstet Gynecol. 2013 May;121(5):943–50.
13. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis.
14. Endometrial Hyperplasia [Internet]. [cited 2023 Feb 22]. Available from: https://www.acog.org/en/womens-health/faqs/endometrial-hyperplasia
15. Gompel A. Progesterone and endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2020 Nov;69:95–107.

How to cite this article: Ervina Pratiwi. Endometrial hyperplasia as an endometrial cancer risk factor: review article. *International Journal of Research and Review*. 2023; 10(3): 289-295.
DOI: *https://doi.org/10.52403/ijrr.20230333*

******