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REVIEW

A Review of the Risk Factors Associated with Endometrial Hyperplasia During Perimenopause

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Background: Endometrial hyperplasia, characterized by excessive growth leading to endometrial thickening, is commonly observed in the premenopausal period. Its prevalence in postmenopausal women is approximately 15%, peaking between ages 50 and 60. This condition often manifests as abnormal uterine bleeding and can progress to malignancy, with varying risks depending on the type of hyperplasia.

Purpose: This study aims to investigate the factors influencing endometrial thickness during the perimenopausal period and raise awareness among healthcare professionals about the importance of evaluating and caring for individuals with endometrial hyperplasia.

Methods: Studies examining the association between various factors such as diabetes mellitus, hypertension, age, estrogen replacement therapy, anovulatory disorders, smoking, medications, genetic factors, and endocrine-related proteins and the development of endometrial hyperplasia were reviewed. The literature search encompassed relevant databases, including PubMed, Scopus, and Web of Science.

Results: Research findings indicate significant associations between changes in gene expression of several factors and the development of endometrial hyperplasia. Notably, the risk of progression to cancer varies between non-atypical and atypical hyperplasia cases. Factors such as diabetes mellitus, hypertension, age, estrogen replacement therapy, anovulatory disorders, smoking, medications, Lynch syndrome, tamoxifen use, and alterations in gene expression of TNF-α, EGF, IGF-1, IGF-1R, and PTEN have been implicated in the pathogenesis of endometrial hyperplasia.

Conclusion: This study underscores the importance of understanding the factors influencing endometrial thickness during the perimenopausal period. It emphasizes the pivotal role of healthcare professionals in evaluating and caring for individuals with this condition.

Keywords: endometrial hyperplasia, premenopausal period, postmenopausal women, pathogenesis, malignancy risk

Introduction

The endometrium is an epithelial layer located inside the uterus and is a dynamic tissue undergoing various changes in a woman of reproductive age.[1,2] These changes include proliferation, secretion, and menstruation. There exists a complex interaction between the female sex hormones estradiol and progesterone. While estradiol stimulates the thickening of the uterus, progesterone promotes differentiation and secretion of epithelial cells.[3–5] The delicate balance between endometrial proliferation and apoptosis is influenced by hormonal and molecular factors as well as environmental factors such as age. Therefore, the endometrial tissue is predisposed to various abnormalities.[6]

Perimenopause generally refers to the transition period from premenopause to menopause in women.[7–9] The average duration of this period varies between 4 and 11 years, starting from the last menstrual cycle.[10] While most women show menopausal symptoms in their 40s, some exhibit symptoms in their 50s, and only 10% show symptoms in their 30s.[7,11,12]

Endometrial hyperplasia (EH) is a condition commonly seen in the menopausal period, characterized by thickening of the endometrial tissue.[13] EH can be diagnosed in women with postmenopausal bleeding. An endometrial thickness of more than 5 mm in women with postmenopausal bleeding is an undesirable condition, and asymptomatic postmenopausal

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women with increased vascularity or endometrial thickness exceeding 11 mm should be evaluated for malignancy risk.[14,15] EH is observed in 15% of postmenopausal women, with its peak occurrence between the ages of 50 and 60. EH develops in 1.3% of women of reproductive age.[13,16]

Common symptoms of EH include menorrhagia, intermenstrual bleeding, postmenopausal bleeding, and abnormal uterine bleeding during hormone replacement therapy or tamoxifen use.[13] Some types of EH may be associated with abnormal epithelial cell proliferation and a tendency to spread to stroma and surrounding tissues, increasing the risk of malignancy.[17–20] Studies have investigated the risk factors associated with EH, but further research is needed.[13,16,21–26] Evaluation and risk assessment of women in the perimenopausal period are also critical.

Early detection of endometrial hyperplasia can reduce mortality from endometrial carcinoma, decrease oncology treatment costs, and contribute to the effective utilization of resources. This review aims to identify risk factors that may contribute to endometrial hyperplasia and emphasize the importance of early diagnosis. Additionally, increasing awareness among healthcare professionals working in women's health regarding endometrial hyperplasia and its risk factors is crucial.

Risk Factors for Endometrial Hyperplasia (EH) During the Perimenopausal Period

Regulation of Endometrial Function by Gonadal Hormones and Implications for EH

Gonadal hormones are secreted in a regulated manner throughout the menstrual cycle, regulating the functions of the endometrium. Endometrial thickness is minimal at the end of menstruation, increases during the follicular phase due to estradiol secretion from the dominant follicle, and reaches maximum thickness in the mid-luteal phase due to increased glandular secretion influenced by progesterone.[27] Estrogens play a role in regulating events such as endometrial cell proliferation, angiogenesis, and inflammation.[28,29] In addition to promoting endometrial cell proliferation, estrogen hormones induce morphometric changes, including alterations in glandular epithelial type, gland numbers and shapes, gland-to-stroma ratio, and epithelial cell morphology.[13,30]

EH results from changes in the shape and size of glandular tissue and an increase in the endometrial gland-to-stroma ratio, representing a pre-cancerous, non-physiological, and non-invasive proliferation of the endometrium.[17–19] According to the World Health Organization's 2014 classification, EH is divided into two groups: non-atypical (endometrial intraepithelial neoplasia/EIN) and atypical endometrial hyperplasia.[31] Non-atypical hyperplasia are benign changes that regress when hormonal changes or endocrine disorders return to normal. However, if endocrine disorders persist long-term, invasive disorders may develop. Atypical endometrial hyperplasia contain many of the mutations typical of invasive endometrioid endometrial cancer (EC).[31] EH is clinically characterized by abnormal uterine bleeding, especially in women.[13] Pathologically, some types of endometrial hyperplasia can be precursors to malignancy.[32] It is noted that the risk of untreated EH progressing to cancer can range from 3% in cases of non-atypical EH to 29% in cases of atypical EH.[33]

AEH is recognized as a precancerous lesion with a significantly higher risk of progression to endometrial carcinoma (EC) compared to non-atypical EH. AEH is associated with a 29% risk of progression to EC, while non-atypical EH carries a much lower risk, approximately 1–3%. This distinction is crucial in clinical decision-making, as AEH often warrants more aggressive treatment, including surgical intervention, whereas non-atypical EH may be managed conservatively.[34]

The International Federation of Gynecology and Obstetrics (FIGO) has recently updated its classification criteria for EC, which now places greater emphasis on the histopathological characteristics of AEH. The new classification recognizes AEH as a distinct entity with a clear progression pathway to EC, necessitating more vigilant monitoring and early therapeutic intervention. This change in classification further reinforces the need to accurately diagnose and appropriately manage AEH to prevent the progression to invasive carcinoma.[35,36]

Chronic stimulation of the endometrial tissue by estrogen due to progesterone deficiency plays a significant role in the development of hyperplasia.[16] EH is considered a precursor to type 1 endometrial carcinoma (EC) and is generally accepted as a precursor to low-grade tumors typically associated with estrogen.[37] Risk factors for EH are similar to those

for type 1 endometrial cancer. Conditions associated with hormonal imbalance, such as polycystic ovary syndrome (PCOS), which causes chronic anovulation, early menarche, late menopause, nulliparity, infertility, and prolonged estrogen use/exposure without progesterone, increase the risk of EH.[16,38] Parity is protective against EC but not against EH.[39] Reproductive factors may differ for EH and EC.[40] EH may occur postmenopausally due to cessation of ovulation and lack of progesterone production in the ovaries, and it may also occur during the perimenopausal period with irregular menstruation.[13]

Furthermore, it has been suggested that the increased development of dominant follicles during the luteal phase, associated with decreased levels of progesterone and inhibin A about advancing age, may contribute to increased endometrial thickness.[21] In the postmenopausal period, estrone (E1), a form of estrogen derived from androgens in adrenal and adipose tissues, replaces estradiol (E2), an ovarian-derived estrogen.[41] Adipocytes in adipose tissue convert adrenal-derived androstenedione to E1 via the action of the aromatase enzyme. Factors such as estrogen replacement therapy, diabetes, history of tamoxifen, and oral contraceptive use are also indicated to be associated with endometrial thickening and endometrial malignancy.[22]

High-Risk Populations for the Development of EH

Two particularly high-risk patient populations for the development of EH have been identified. The first comprises peri- or postmenopausal women who are obese due to excessive adiposity in the abdominal region. This leads to a significant conversion of androgens in adipose tissue to estrogen by the action of the aromatase enzyme.[42] It is known that insulin-like growth factor 1 (IGF-1) and its binding protein (IGF binding protein-1) support endometrial cell growth. Elevated levels of IGF have been reported in obese women, which may contribute to EH development by predisposing them to endometrial cancer.[43] Additionally, in obese women with diabetes mellitus (DM), high insulin resistance has been observed, leading to a decrease in sex hormone-binding globulin (SHBG) concentration due to increased insulin levels, resulting in elevated estrogen levels.[44–46]

The second high-risk group for EH development consists of premenopausal women with polycystic ovary syndrome (PCOS) characterized by hyperandrogenic activity. While endometrial stimulation by estrogens is considered a primary risk factor for EH development, other factors, such as immunosuppression, may also play a role.[42,47] The chronic exposure of the endometrium to high levels of estrogen without the counterbalancing effect of progesterone leads to increased cell proliferation and a heightened risk of malignant transformation.[48]

Most cases of EH occur in the presence of chronic exposure to estrogen, which is not counteracted by progesterone, as seen in conditions like PCOS and obesity.[49] PCOS is a common endocrinopathy associated with insulin resistance, hyperandrogenism, negative cardiovascular risk factors, and infertility-related issues.[50–52] Hyperandrogenism in PCOS can lead to acne, hirsutism, and alopecia. Moreover, due to the conversion of androgens to estrogens and excess estrogen synthesis, ovarian dysfunction, chronic oligomenorrhea, infertility, endometrial hyperplasia, and endometrial cancer can occur.[53–55]

Studies have shown that the risk of EH increases up to threefold in obesity and is a common condition in PCOS, where EH frequency ranges from 35.7% to 48.8%. Furthermore, obesity, diabetes mellitus, and hypertension are associated with EH.[56,57] Obesity-induced chronic inflammation, resulting in increased estrogen levels, is suggested to contribute to EH and malignancy.[13,56,58–64] Additionally, factors such as high BMI and hypertensive and anti-inflammatory drug use, as well as hormone replacement therapy, are associated with EH development.[65,66] Studies differentiate between the effects of steroidal anti-inflammatory drugs, like corticosteroids, which may exert a broader influence on metabolic processes and potentially alter the risk of endometrial hyperplasia (EH), compared to non-steroidal anti-inflammatory drugs (NSAIDs), which primarily target inflammation pathways.[67,68] Additionally, the literature has discussed the impacts of various classes of antihypertensive drugs—such as ACE inhibitors, beta-blockers, and diuretics—on EH risk, providing relevant insights into how these medications may influence the development or management of EH.[67] Research indicates that hypertensive patients often have a higher frequency of endometrial thickening and hyperplasia. A study showed that hyperplasia was the most common positive histological finding among hypertensive women, further supporting the association between hypertension, EH, and the pharmacological agents used to manage these conditions.[67]

However, no significant differences in EH development were found between smokers and non-smokers, individuals with hypertension and normotensives, or individuals with and without diabetes mellitus. While the results regarding age were insufficient, a significant relationship was established between BMI and endometrial hyperplasia, indicating that a high BMI may increase the risk of EH.[69–71]

In postmenopausal women, a study examining factors affecting endometrial thickness found no relationship between diseases such as DM and hypertension and endometrial thickness, but a relationship was observed between BMI, ovarian volume, uterine volume, tamoxifen use, serum E2 levels, and endometrial thickness.[72] Another study found no significant relationship between DM and high BMI and increased endometrial thickness, but a significantly higher endometrial thickness was observed in patients with hypertension and non-smokers. A weak significant relationship was found between hormone replacement therapy and increased endometrial thickness. This study emphasized the importance of BMI as a significant parameter affecting endometrial thickness in postmenopausal women.[73]

In a study comparing the effects of age, endometrial thickness, and BMI on malignancy development in postmenopausal women with postmenopausal bleeding, a significant relationship was found between endometrial thickness and age and malignancy development, while no significant relationship was found between BMI and malignancy. These findings may vary depending on changing diagnostic criteria and the nature of PCOS. The threefold increased risk of EC in PCOS and the connection between EH and EC suggest a relationship between EH and PCOS.[74–77] Recent evidence suggests that asymptomatic women, particularly those with underlying risk factors such as obesity, may still harbor a significant risk of developing EC. The recent findings underscore the need for updated screening guidelines and risk stratification models to identify high-risk individuals who might benefit from early intervention.[78,79]

In hypertensive patients, endometrial hyperplasia (EH) is frequently encountered, and the use of hypertensive medications has been associated with EH development.[21,80–82] It is speculated that diabetes mellitus (DM) may not only cause EH but also predispose existing hyperplasia to malignant transformation. A meta-analysis has shown the likelihood of malignancy in women with DM who have EH.[83] In another study examining the relationship between gestational diabetes mellitus (GDM) and EH and endometrial carcinoma (EC), it was found that GDM is associated with both EH development and EC. However, the relationship between GDM and EC was reported to be stronger than that between GDM and EH.[84] The use of tamoxifen, a selective estrogen receptor modulator (SERM) used in cancer treatment, poses a risk for EH, endometrial polyps, abnormal vaginal bleeding, and EC development due to its estrogenic effect on the endometrium.[85] The studies indicate that women undergoing tamoxifen therapy have an increased risk of developing EH and EC. The mechanism is believed to be related to the agonistic effects of tamoxifen on the endometrial tissue, which may lead to hyperplasia and subsequent malignancy. This risk highlights the necessity of regular endometrial surveillance in patients receiving tamoxifen or similar agents.[86,87] Women with Lynch syndrome may develop atypical EH at an early age, as there are changes in estrogen levels affecting the expression of DNA repair genes in these women.[25] Additionally, peripheral estrogen synthesis may increase due to adrenal cortical tumors that secrete androgens, leading to EH.[13]

Apart from estrogen stimulation of the endometrium, EH can also occur due to other reasons, such as immunosuppression and infection.[88] Endometrial inflammation leads to an imbalance in the cytokine system, developing EH. Inflammation causes a decrease in factors such as tumor necrosis factor-alpha (TNF-α) and epidermal growth factor (EGF), while insulin-like growth factor-1 receptor (IGF-1R) levels increase.[89–91] It has been stated that the expression of IGF-1R is much higher in EH and malignancy cases compared to normal conditions.[92,93] Only in adenomatous hyperplasia has a decrease in the expression of the IGF-1 gene been noted.[89] The synthesis of IGF-1 is induced by estradiol and affects uterine growth.[94] Another factor in EH development is phosphatase and tensin homolog (PTEN). PTEN is a tumor suppressor gene located on chromosome 10q23, encoding a phosphatase with protein and lipid effects. As an antagonist in cell signaling pathways induced by growth factors, PTEN regulates cell proliferation and apoptosis.[95,96] While PTEN expression increases in both glandular epithelium and stromal compartments during the proliferative phase, it decreases in the glandular epithelium compartment during the secretory phase.[97] A mutation causing loss of function in the PTEN gene may lead to upregulation of endometrial glandular proliferation and is associated with EH and cancer development.[26,98] Among cases, isolated PTEN-null glands have been shown in 43% of

macroscopically standard premenopausal endometrial samples. Due to genetic mutation and deletion, these glands cannot express the PTEN protein and are mainly found between menstrual cycles.[99]

Endometrial hyperplasia is essential not only due to the damaging physical and psychological symptoms it causes but also because it can be a precursor to cancer. The risk of endometrial hyperplasia progressing to cancer can range from 3% in cases of non-atypical EH to 29% in cases of atypical EH.[33] At this point, evaluating risk factors that may lead to the development of endometrial hyperplasia and intervening early can be lifesaving.[100–103]

Conclusion

A myriad of risk factors influence endometrial hyperplasia. Research has extensively explored various contributors, including diabetes mellitus (DM), hypertension (HT), age, estrogen replacement therapy, anovulatory disorders such as polycystic ovary syndrome (PCOS), smoking, medical treatments, Lynch syndrome, and tamoxifen use. Among these, obesity has emerged as a particularly significant factor in the development of endometrial hyperplasia. Additionally, studies have examined the relationship between genetic expression changes—specifically in genes such as TNF-α, EGF, IGF-1, IGF-1R, and PTEN—and the onset of endometrial hyperplasia. Notably, IGF-1 and PTEN are thought to play pivotal roles. However, despite extensive research on these risk factors, further studies are necessary to achieve more comprehensive and conclusive results.

Given that certain types of endometrial hyperplasia can cause significant physical and psychological distress and serve as precursors to cancer, early intervention is essential for long-term health. With the rising incidence of endometrial hyperplasia during the postmenopausal period, it is critical to conduct thorough evaluations of women during this time. Additionally, comprehensive assessments and risk evaluations should be carried out during the premenopausal period. Early detection and intervention in cases of malignancies associated with endometrial hyperplasia can alleviate the physical and economic burden on patients, enhance women's health, and reduce mortality rates related to endometrial cancer.

Disclosure

The authors report no conflicts of interest in this work.

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