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Endometrial Hyperplasia as an Actionable Precursor to Endometrial Cancer: Narrative Review

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Гіперплазія ендометрію як мішень для вторинної профілактики ендометріального раку: огляд літератури

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Introduction

Endometrial cancer (EC) represents the most prevalent malignancy within the spectrum of gynecologic oncological diseases, underscoring its status as a critical global public health concern [1]. According to GLOBOCAN statistics, EC occupies the sixth position in the overall structure of oncological diseases affecting women [2], with both incidence and mortality continuing an upward trajectory worldwide [3]. In 2024, more than 460,000 new cases of EC were identified globally, reflecting an average annual incidence increase of 4.1% [4]. Geographic disparities in disease burden remain pronounced: the highest incidence rates were documented in the United States (66.2 per 100,000 women) and Western Europe (20.2 per 100,000 women) [5]. In Ukraine National Cancer Registry statistics demonstrate that the incidence of EC increased from 27.9 per 100.000 women in 2017 [6] to 34.2 per 100.000 women in 2022 [7], reflecting a 22.6% rise within five years. This accelerating trend is tightly linked to broader demographic and epidemiological shifts, including population aging and the rising prevalence of metabolic health disorders. Although EC predominantly affects perimenopausal and postmenopausal women – with a mean age of onset at 55 years – the age profile is shifting toward younger cohorts [8]. Current data indicate that women aged 45–54 account for 16.7% of new diagnoses, while those aged 55–64 and 65–74 represent 34.5% and 25.8% of cases, respectively [9]. In terms of mortality, EC was responsible for approximately 97,000 deaths worldwide in 2022. Global health equity disparities are evident in these outcomes: the age-standardized mortality rate was significantly higher in low- and middle-income countries (3.2 per 100,000 women) than in high-income countries (1.8 per 100,000 women) [2], illustrating substantial gaps in healthcare infrastructure, population health literacy, and access to timely screening and diagnostic services. In Ukraine, EC caused approximately 1,912 deaths in 2022, corresponding to an age-standardized mortality rate of 0.48 per 100,000 women [2].

From a public health and health economics perspective, survival outcomes and clinical resource utilization are heavily dependent on the stage at EC diagnosis. The EUROCARE-6 study reported the estimated number of EH survivors in Europe to be 123,000 within the past 2 years, 159,000 within the past 2–5 years, and 650,000 for more than 5 years (long-term survivors) [10]. Patients diagnosed at an early stage typically undergo curative primary surgical intervention, achieving a 5-year survival rate of 90% and a low recurrence risk of 10-15%. Conversely, 20-25% of patients present with advanced disease, where 5-year survival drops to approximately 40% and recurrence rates surge to 40–70% [11].

Consequently, the primary window for reducing population mortality lies in early detection and secondary prevention of EC. Central to effective secondary prevention is the management of precursor lesions, specifically endometrial hyperplasia (EH). Pathologically, EC is broadly categorized into endometrioid (Type I, accounting for ~80% of cases) and non-endometrioid (Type II, ~20%) subtypes. Crucially, endometrioid EC develops almost exclusively along a continuum originating from atypical EH [12]. EH and EC share key modifiable and non-modifiable risk drivers, including obesity, type 2 diabetes mellitus (T2DM), hypertension, polycystic ovary syndrome (PCOS), unopposed exogenous estrogen exposure, and infectious agents [13–15]. Because these precursor lesions represent a detectable and treatable pre-malignant phase, identifying high-risk population cohorts and implementing structured early detection protocols in primary and outpatient care offer a high-impact, cost-effective strategy to alleviate the overall burden of EC.

The purpose of the research is to evaluate endometrial hyperplastic disorders as an actionable precursor to EC from a public health perspective, analyzing risk determinants, early detection triage mechanisms, and population-based prevention strategies.

Object, materials and research methods

We employed general scientific methodologies, including comprehensive literature search, analytical review, synthesis, and thematic generalization. This manuscript was prepared as a **narrative review** focusing on the epidemiological burden, clinical symptoms, risk determinants, early detection and population-based prevention strategies associated with EH as a precursor to EC. A literature search was performed in PubMed and Google Scholar, using terms including *"endometrial cancer"*, *"epidemiology"*, *"abnormal uterine bleeding", "risk factors"*, *"endometrial hyperplasia"*, "health disparities*", "early detection", "screening", "prevention"*. The search covered publications published in English and Ukrainian from 2002 to 2026, with emphasis on recent epidemiological studies, national health registries, and global health guidelines to capture evolving public health approaches. Inclusion criteria: original research articles, population-based cohort studies, clinical trials, systematic reviews, meta-analyses, and authoritative consensus guidelines evaluating EH epidemiological risk factors, screening/triage protocols, public health impacts, or early detection strategies for preventing progression to EC. Exclusion criteria: case reports, conference abstracts without full text, non-English and non-Ukrainian publications, and studies lacking relevance to EH or its progression to EC.

Research results

Definition, Epidemiology, and Risk Stratification of EH

EH comprises a spectrum of non-invasive proliferative alterations within the uterine mucosal lining, characterized morphologically by glandular structural crowding and an abnormal increase in the gland-to-stroma ratio exceeding 50% [16]. Pathologically, EH represents a disordered proliferation of endometrial glands that typically arises in the setting of continuous, unopposed estrogenic stimulation coupled with a relative or absolute deficiency of counterbalancing progesterone [17]. Under persistent estrogenic drive, endometrial tissue undergoes accelerated cellular division, acquiring proliferative autonomy and structural remodeling [18].

From an epidemiological perspective, EH represents a widespread yet frequently underdiagnosed clinical condition. There are data that EH affects approximately 15% of postmenopausal women – peaking between 50 and 60 years of age – and occurs in 1.3% of women of reproductive age [19]. In high-income countries, approximately 200,000 new cases of EH are recognized annually. However, establishing precise global incidence rates remains challenging due to variable diagnostic criteria, differing national hormone therapy prescribing practices, and frequent co-occurrence with occult invasive malignancy [20]. In many middle-income and developing nations, including Ukraine, systemic surveillance is further limited by the absence of localized health registry tracking for non-malignant precursor lesions [21].

It is of critical importance to underscore that EH is not a single pathological entity; rather, it includes both hyperplasia without atypia, which carries a low malignant potential, and premalignant lesions such as atypical hyperplasia and endometrial intraepithelial neoplasia (EIN) [22]. The distinction between well-differentiated EIN and atypical EH is based on the presence of stromal invasion, characterized by the loss of intervening stroma. Histologically, atypical EH consists of crowded aggregates of altered tubular or branched glands, which are cytologically distinct from the background structural and cytological pattern. In areas of atypical EH, glands predominate over stroma, leading to a reduction in stromal volume [23; 24]. Occasionally, changes characteristic of EH may be represented by a small focus within the endometrium that, by all other criteria, does not appear hyperplastic. In such cases, the term 'focal hyperplasia' should be applied [8]. A. Travaglino et al. suggested that EH may be a polyclonal proliferative lesion or a monoclonal precancerous lesion, differentiated on the basis of cytologic atypia by 2014 World Health Organization system, which classified EH into two groups due to limited clinical utility and poor reproducibility: (i) non-atypical hyperplasia, associated with a low risk of malignant transformation (approximately 1–3%), and (ii) atypical hyperplasia/EIN, which has a significantly higher risk of progression (25–40% if left untreated [25; 26]. Viewing this histological classification through a public health lens transforms atypical EH/EIN from a microscopic diagnosis into a critical, actionable secondary prevention target. Identifying women with EIN provides healthcare systems with a distinct window of opportunity to intervene prior to the onset of invasive, life-threatening malignancy.

Clinical Presentation and Early Detection Triage

The public health impact of EH is closely tied to its clinical presentation and the efficiency of outpatient diagnostic triage. Abnormal uterine bleeding (AUB), vaginal fluid, uterine cavity fluid, and hypogastric pain represent the key symptoms of EH [27]. AUB, resulting in iron-deficiency anemia, is the most common clinical symptom of EH, which significantly impairs women's health, working capacity and quality of life, and in certain cases may contribute to premature mortality [28]. On the other hand, approximately one-fifth of patients referred to the obstetric clinic with AUB have been diagnosed with EH [29]. Menorrhagia, oligomenorrhea, or intermenstrual spotting are some of the symptoms that premenopausal women may experience, while postmenopausal women should be evaluated for even one vaginal bleeding episode [30].

A central challenge in early detection is that EH can present with subtle, non-specific, oligosymptomatic or entirely asymptomatic courses, leading to the progression of the disease and the development of severe complications. Typically, such clinical cases are occasionally discovered by chance when an endometrial sample or pelvic imaging

is performed for other purposes [21; 31]. Transvaginal ultrasonography (TVUS) provides an accessible, non-invasive primary screening tool. An endometrial thickness of more than 5 mm in women with postmenopausal bleeding is an undesirable condition, and asymptomatic postmenopausal women with increased vascularity or endometrial thickness exceeding 11 mm should be evaluated for malignancy risk [19]. In-office endometrial sampling offers a low-cost, minimally invasive alternative to inpatient fractional curettage, reducing healthcare costs while maintaining high diagnostic accuracy.

Although the definitive diagnosis of EH relies exclusively on morphological examination of endometrial specimens, differential diagnosis extends beyond morphology and incorporates a wide range of modern investigative laboratory techniques. These include biochemical assays, immunohistochemical and immunocytological methods, in situ hybridization, polymerase chain reaction, laser microdissection, and microarray technologies. Such approaches enable the study of proteins regulating apoptosis and mitotic activity, tumor suppressor and promoter genes, growth factors and their receptors, interleukins, cytokines, and other regulatory systems at the cellular level. Collectively, these advanced methodologies provide a more comprehensive understanding of the molecular and cellular mechanisms underlying EH, thereby enhancing diagnostic accuracy and informing therapeutic strategies [32].

Population Risk Determinants

The Syndemic of Obesity and Metabolic Dysfunction

The rising incidence of EH and subsequent EC mirrors global trends in obesity and metabolic syndrome, creating a major public health syndemic [22; 33]. Excess adipose tissue functions as an active endocrine organ, significantly altering systemic hormone kinetics and metabolic homeostasis. It leads to a reduction in anti-inflammatory cytokines while simultaneously increasing the secretion of pro-inflammatory adipokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). This imbalance fosters chronic low-grade inflammation, which sustains a protumorigenic microenvironment. Cytokine-mediated signaling cascades, together with oxidative stress, damage endometrial cellular structures and promote mutagenesis. Furthermore, obesity is associated with increased expression of Fas mRNA and the insulin-like growth factor-1 (IGF-1) receptor, both of which significantly influence apoptosis and cellular proliferation. These molecular alterations impair DNA repair mechanisms within endometrial cells, thereby heightening the risk not only of hyperplasia but also of subsequent malignant transformation [34].

In addition, in obese women, a high amount of adipose tissue is closely associated with higher local and circulating levels of estradiol. This can be explained through various mechanisms. Firstly, an increase in adrenal secretory activity is often observed, which leads to an increase in androgen precursors. These precursors may then be converted to estradiol in peripheral tissues. Secondly, the conversion rate of androstenedione to estrone by the enzyme aromatase rises as this conversion primarily takes place in adipose tissue (particularly in postmenopausal women). Lastly, higher concentrations of estradiol can be found in obese patients as plasma levels of estradiol-binding sex hormone-binding globulin (SHBG) are typically depressed in this patient population [35; 36]. G.E. Hale et al. found that increased conversion of androstendione to estrone by tissue aromatase, increased free estrogen due to decreased SHBG, increased insulin-like growth factor, and decreased progesterone secondary to ovulation disorder relative to baseline are mechanisms of increased risk of obesity-associated endometrial lesions [37].

At the population level there are data that obesity increases the risk of endometrial malignancy two- to five-fold depending on body mass index (BMI) [38]. A. Mihaylova et al. identified BMI as an independent predictor of EIN/EC (OR=1.29; p=0.015) [39]. Furthermore, T2DM and insulin resistance exert direct mitogenic effects on the endometrium through hyperinsulinemia and altered growth factor signaling, increasing disease risk two- to four-fold independently of BMI [40; 41]. It should be noted that insulin resistance is usually indicated not as isolated symptom, but as the core symptom of metabolic syndrome, which induced a chronic inflammatory state, manifested by excessive local expression of TNF-α, IL-6 and reactive oxygen species, resulting in persistent stimulation of endometrial cell hyperplasia [42]. Y. Ding et al. found that metabolic syndrome was remarkably related to disordered proliferative endometrium, EH and EC [43]. Consequently, comprehensive metabolic management represents a core component of primary prevention of endometrial hyperplastic disorders.

Reproductive Factors and Unopposed Endocrine Exposures

The endometrium is extremely susceptible to changes in sex steroid hormones. Estrogen promotes the growth of endometrial glands, while progesterone inhibits mitotic activity and induces secretory differentiation. T.A. Fasha et al. suggested that estrogen plays a central role by stimulating local proliferation of endometriotic tissue, whereas progesterone resistance contributes to impaired apoptosis and aberrant inflammatory signaling [44]. That's why the most significant risk factor for the development of EH remains the prolonged or excessive exposure to estrogen occurring against the background of either relative or absolute insufficiency of progesterone production, or diminished receptor sensitivity to this hormone (often referred to in clinical practice as "unopposed") [45].

Lifetime reproductive history significantly influences individual susceptibility to EH by dictating total cumulative exposure to unopposed estrogen [46]. Nulliparity, late menopause (usually described in those aged 55 and older), and early menarche (typically defined in individuals younger than 12) increase risk by extending the duration of unopposed estrogen action [47].

Chronic anovulation is another important risk factor for EH. When anovulation occurs, sex hormone production

is not cyclical as in regularly ovulating premenopausal women. Without ovulation, estrogen levels still dominate without the opposing effect of progesterone produced by the corpus luteum after ovulation. This imbalance leads to a continued proliferation of the endometrium resulting in a higher risk of developing EH and eventually endometrioid EC. Common settings associated with anovulation include polycystic ovary syndrome (PCOS), hyperprolactinemia, and perimenopausal hormonal status [46; 48].

Hormone-secreting tumors can also cause an endogenous sex hormone imbalance. For example, granulosa cell tumors represent potentially estrogen-secreting tumors of the ovary [46]. There are data that up to 80% of granulosa cell tumors can produce estrogen, which can cause EH. In addition, it has variable atypia in 24% to 80% of cases, and up to 5% are associate with endometrial adenocarcinoma [49].

Exogenous estrogen exposure, particularly in the form of unopposed estrogen therapy administered to women with an intact uterus, has been consistently associated with an increased risk of EH and subsequent progression to EC. This elevated risk has been documented in both premenopausal and postmenopausal women, underscoring the pathogenic potential of estrogen stimulation in the absence of concomitant progestogenic regulation. The absence of progesterone-mediated counterbalance facilitates continuous endometrial proliferation, thereby creating conditions conducive to atypical hyperplastic changes and malignant transformation [46]. Moreover, tamoxifen (selective estrogen receptor modulator) is associated with dose- and time-dependent increases in the risks of endometrial proliferation and hyperplasia, as well as uterine sarcoma [50; 51].

Psychosocial Stress, Lifestyle, and Systemic Vulnerabilities

Lifestyle-related risk factors such as physical activity, smoking status, alcohol intake, sleep duration, dietary habits (high intake of saturated fats, refined carbohydrates, and ultra-processed foods) and chronic stress also play an important role in the development of precursor and malignant endometrial conditions [39]. Chronic stress is increasingly recognized as a contributing risk factor for both EH and EC, primarily through its effects on hormonal regulation, immune function, and tumor biology. Cortisol, a typical glucocorticoid hormone, is produced and secreted by the zona fasciculata of the adrenal cortex from cholesterol via pregnenolone and progesterone, and regulates carbohydrate, fat, and protein metabolism. When the body is stressed, the hypothalamic–pituitary–adrenal cortical axis is activated, and the secretion of cortisol is enhanced; thus, cortisol is positioned as a stress hormone [52]. The consequent increase in cortisol triggers a wide variety of physiological effects to help the body cope with stress, including increasing blood glucose levels, mobilizing fat and protein to provide additional energy, suppressing the immune system and inflammation, increasing cardiovascular responsiveness to epinephrine and norepinephrine, and increasing cognitive alertness [53]. T.A. Fasha et al. suggested that dysregulation of the hypothalamic–pituitary–adrenal cortical axis, manifesting as initial hypercortisolism followed by adaptive hypocortisolism, has been proposed as a feature of chronic inflammatory conditions, including endometrial pathology [44].

Cortisol is also a potent anti-inflammatory agent with immunosuppressive properties and has also been implicated as playing a role in tumorigenesis, particularly in gynaecological cancers [54]. The results of Mendelian randomization studies on EC showed that DM type 2, uterine fibroids, higher BMI, higher plasminogen activator inhibitor-1, higher fasting insulin, early insulin secretion, longer telomere length, higher testosterone and higher plasma cortisol levels are associated with increased risk of EC. In contrast, later age of menarche, higher circulatory TNF-α, higher low-density lipoprotein cholesterol, and higher SHBG levels are associated with reduced risk of EC [55], highlighting the importance of addressing stress and lifestyle factors within public health frameworks.

Evidence suggests links between chronic stress and cancer progression, with the cortisol and its glucocorticoid receptor (GR) as prominent mediators of the human stress response inducing pro-survival pathways in epithelial tumour cells [56]. GR signaling is a central physiological mechanism that integrates endocrine cues to regulate metabolism, immunity, and stress responses [53]. The GR belongs to the nuclear receptor superfamily and is a ubiquitously expressed ligand activated transcription factor. In the absence of a ligand, the GR resides in the cell's cytoplasm as a monomer, part of a large multiprotein complex that includes HSP90, immunophilins (e.g., FKBP51 and FKBP52) and other chaperone proteins [57; 58]. Moreover, the GR shares structural homology, chromatin binding sites, and co-regulatory networks with the estrogen receptor. Consequently, the functional impact of GR signaling in estrogen-responsive malignancies, particularly endometrial tumours, is dependent on estrogen receptor expression and activity. In EC, expression of the GR is associated with a worse prognosis, but only in tumours that express high levels of estrogen receptor [59; 60].

Chronic Inflammatory Co-Factors and Infectious Agents

Chronic tissue hypoxia and localized inflammatory signaling act as additional co-factors in endometrial transformation [32; 61]. Persistent hypoxia has been shown to impair energy metabolism, suppress the synthesis of biologically active substances, and simultaneously stimulate angiogenesis and growth factors, while enhancing transmembrane glucose transport and glycolytic metabolism. In addition, hypoxia activates a range of transcription factors, particularly hypoxia-inducible factors, which promote cellular proliferation and attenuate apoptosis. From an infectious standpoint, a thin atrophic endometrium constitutes a favorable nutrient environment. Prolonged inflammation contributes to stromal fibrosis and fiber hyalinosis,

and obstruction of the excretory ducts within epithelial glands results in cystic dilatations. Within the pathogenesis of EH, chronic inflammation functions as a persistent driver of cellular proliferation, apoptosis dysregulation, and tissue remodeling, thereby establishing a microenvironment that facilitates the progression of hyperplasia toward atypical forms. Elevated concentrations of interleukin-1 beta (IL-1β), IL-6, and TNF-α in endometrial tissue further stimulate cellular proliferation and angiogenesis; these cytokines perpetuate chronic inflammation and confer resistance to apoptosis. Moreover, chronic inflammation amplifies the effects of local hyperestrogenism, which remains the primary etiological factor in the development of EH [61].

Epidemiological evidence also suggests a link between persistent lower genital tract infections, such as Human Papillomavirus (HPV) and *Chlamydia trachomatis* (CT), and chronic inflammatory endometrial alterations [13–15]. In particular, H. Gautam et al. investigated the prevalence of HPV and CT among North Indian women diagnosed with cervical carcinoma and EC [13]. The authors identified a high prevalence of HPV in cervical cancer tissue (72%), driven predominantly by the HPV-16 genotype, whereas HPV detection in endometrial carcinoma was low (5%) and restricted entirely to pre-cancerous tissues. CT infection was detected in approximately 10% of cervical cancer patients and 5–8% of endometrial cases. Review by R. Rodrigues et al. highlights several key cellular pathways modulated by CT, including the induction of chronic inflammatory responses, host DNA damage, inhibition of host-cell apoptosis, genomic instability, and structural remodeling of the extracellular matrix and cell-cell junctions [14]. The authors conclude that CT functions primarily as a co-factor, often operating synergistically with high-risk HPV – to establish a permissive microenvironment for neoplastic transformation rather than acting as a direct, solitary carcinogen. These findings suggest that integrating routine lower genital tract infection management into primary reproductive healthcare may offer secondary benefits for endometrial health.

Genetic Factors

Other risk factors include inherited genetic conditions such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer) and Cowden syndrome [46]. These syndromes account for a distinct, high-risk population cohort that requires structured genetic counseling, targeted surveillance, and cascade screening protocols within public health systems. Although hereditary cases represent a minority of total EC diagnoses, identifying affected families provides a high-yield opportunity for secondary and primary cancer prevention.

Lynch syndrome (an autosomal dominant inherited disorder caused by mutations in mismatch repair genes), associated with a markedly increased lifetime risk of EC, frequently involves EH as a precursor lesion. There are data that women with Lynch syndrome have an approximately 40%–60% chance of presenting a sentinel EC, which is the most common extraintestinal sentinel cancer in Lynch syndrome patients. In addition, patients with Lynch syndrome-related EC have a 25% estimated risk of developing a second malignancy within 10 years and a 50% risk within 15 years after the initial EC diagnosis [62; 63]. From a public health standpoint, implementing universal reflex mismatch repair screening (via immunohistochemistry or microsatellite instability testing) on all endometrial biopsies and surgical specimens enables early identification of index cases and triggers family-level cascade genetic testing. Surveillance for EC in carriers of Lynch syndrome mutations should generally start at age 30 years; however, individual factors must be considered. ESGO-ESTRO-ESP guidelines for the management of patients with EC: update 2025 suggest that surveillance of the endometrium with annual transvaginal ultrasound and annual or biennial biopsy until hysterectomy should be considered in all carriers of Lynch syndrome mutations. Hysterectomy and bilateral salpingo-oophorectomy to prevent endometrial and ovarian cancer by minimally invasive surgery should be offered once the patient has decided not to have children or further children and preferably before age 40 years in patients with *MLH1*, *MSH2*, or *MSH6* mutations. Hysterectomy and bilateral salpingo-oophorectomy are recommended at the time of menopause in patients with *PMS2* mutations [64].

Cowden syndrome, which is rare and, in most cases, related to a mutation in the phosphatase and tensin homologue deleted on chromosome 10 (PTEN) gene, located on chromosome 10q23.31, is strongly associated with an elevated risk of EC, alongside breast and thyroid malignancies. Women with Cowden syndrome often present with recurrent endometrial polyps, which can progress to carcinoma, warranting vigilant surveillance and preventive strategies [65]. It should be noted that PTEN loss occurs in approximately 40–60% of atypical EH compared to 15–30% of non-atypical EH [31].

Discussion of research results

The synthesis of current evidence underscores EH not merely as a localized histological alteration, but as a complex pathophysiological continuum driven by persistent, unopposed estrogenic stimulation. Pathologically, the transition from cellular proliferation to architectural crowding (exceeding a gland-to-stroma ratio of 50%) highlights the loss of homeostatic regulation in the uterine mucosal lining [16–18]. Epidemiologically, the burden of EH remains substantial, affecting approximately 15% of postmenopausal women and over 1% of women of reproductive age. However, true global disease metrics are frequently obscured by regional variations in diagnostic criteria, differing hormone replacement therapy protocols, and the frequent coexistence of occult invasive lesions. This diagnostic discrepancy is particularly pronounced in middle-income and developing nations, such as Ukraine, where the lack of localized, registry-based tracking for non-malignant precursor lesions presents a significant barrier to

public health surveillance [19–21]. Addressing this burden requires optimizing outpatient diagnostic triage. Because clinical presentation ranges from overt AUB – frequently complicated by iron-deficiency anemia – to entirely asymptomatic or oligosymptomatic presentations [27–31], primary care and gynecological triage protocols must maintain low thresholds for investigation. TVUS serves as a key frontline screening tool, using established endometrial thickness cut-offs (>5 mm in postmenopausal bleeding; >11 mm or hypervascularity in asymptomatic individuals) to guide triage. Furthermore, transitioning toward in-office endometrial sampling provides a cost-effective, high-accuracy alternative to inpatient fractional curettage. To refine risk stratification beyond traditional morphology, the integration of advanced molecular assays – including immunohistochemistry, polymerase chain reaction, and microarray profiling – promises to better identify apoptotic dysregulation and mitotic markers, tailoring management before overt malignant transformation occurs [32].

The rising global prevalence of EH and EC closely parallels the expansion of obesity, T2DM, and metabolic syndrome, forming a multi-system syndemic. Visceral adipose tissue functions as an active endocrine organ, driving peripheral conversion of circulating androstenedione to estrone via enhanced aromatase expression while simultaneously suppressing SHBG synthesis. This dysregulation elevates bioavailable free estradiol, maintaining continuous proliferation of the endometrial baseline. Concurrently, metabolic dysfunction fuels direct mitogenic pathways; hyperinsulinemia and altered IGF-1 signaling stimulate cellular division and attenuate repair mechanisms independently of BMI [34–41]. This complex signaling network emphasizes that primary prevention of EH requires comprehensive clinical approaches that combine weight management and metabolic control alongside traditional gynecological care.

Chronic tissue microenvironment dysregulation is further exacerbated by localized infectious and inflammatory factors. Persistent infections of the lower genital tract, such as CT and high-risk HPV, act as co-factors in endometrial transformation [13–15]. Although HPV integration within the endometrium remains low relative to cervical tissues, CT infection induces host DNA damage, impairs apoptosis, and causes extracellular matrix remodeling. Synergizing with chronic hypoxia and hyperestrogenism, these infectious agents maintain persistent stromal inflammation, fibrotic hyalinosis, and cystic glandular dilatation, supporting a microenvironment conducive to neoplastic progression [14; 61]. Consequently, identifying and managing lower genital tract infections represents a relevant secondary health measure for long-term endometrial stability.

In addition, hereditary cancer syndromes identify a distinct, high-risk cohort requiring structured precision management. Lynch syndrome – caused by germline mutations in mismatch repair (MMR) genes presents a 40–60% lifetime risk of sentinel EC, frequently preceded by EH. Integrating universal reflex MMR screening via immunohistochemistry or microsatellite instability testing on all endometrial biopsies serves as an effective diagnostic entry point, facilitating cascade testing across affected families. Similarly, Cowden syndrome – driven by germline *PTEN* mutations – presents an elevated risk for recurrent endometrial polyps and neoplastic transformation. Given that somatic *PTEN* loss occurs in up to 60% of atypical EH cases compared to 15–30% of non-atypical EH, *PTEN* dysregulation serves as a core biomarker marking the transition from polyclonal benign proliferation to monoclonal pre-malignancy [31; 62–65].

Thus, to effectively mitigate the global and regional burden of EC, healthcare systems must transition from reactive management of advanced malignancies toward an integrated, population-based prevention framework centered on EH. At the primary prevention level, risk-factor mitigation necessitates embedding metabolic, lifestyle, and stress management interventions into primary care to attenuate obesity-driven hyperestrogenism, alongside rational prescribing guidelines for opposed estrogens and tamoxifen monitoring. Secondary prevention relies on elevating public symptom literacy regarding abnormal uterine bleeding among perimenopausal and postmenopausal women, facilitating prompt clinical presentation. Concurrently, expanding outpatient diagnostic triage via transvaginal ultrasound and endometrial sampling circumvents unnecessary inpatient curettage while enabling targeted surveillance for high-risk genetic and metabolic cohorts. At the tertiary level, implementing risk-stratified clinical pathways ensures that non-atypical EH receives conservative medical management, whereas atypical hyperplasia and EIN are systematically triaged toward definitive surgical or specialized fertility-sparing protocols. Ultimately, establishing localized and national precursor registries will prove vital for monitoring EH morbidity, evaluating real-world treatment outcomes, and sustaining long-term population-level follow-up.

Prospects for further research

Further research must bridge current knowledge gaps between epidemiological insights and health system execution. Key public health research priorities include: validation of triage prediction models (developing and validating low-cost clinical risk score algorithms integrating BMI, age, metabolic parameters, ultrasound findings, and AUB patterns to assist primary care providers in triaging patients for endometrial sampling); evaluating the cost-effectiveness and feasibility of scaling outpatient endometrial sampling and localized TVUS triage in low- and middle-income healthcare settings, particularly in Ukraine; biomarker discovery and translating molecular insights into accessible, non-invasive triage tests (e.g., cervical brushings or liquid biopsy assays) to refine population risk stratification; epidemiological surveillance enhancement (establishing systematic registry tracking for non-malignant precursor lesions (atypical EH/EIN)

to capture true incidence rates, address regional health disparities, and evaluate the long-term impact of public health prevention programs).

Conclusions

EH constitutes a spectrum of abnormal endometrial proliferative changes ranging from benign glandular overgrowth to precancerous lesions, among which atypical EH/EIN represents an actionable pre-malignant phase along the continuum toward EC. Disease progression is driven primarily by unopposed hyperestrogenism closely linked to obesity and metabolic syndrome. This estrogenic drive is further amplified by chronic HPA-axis stress signaling, persistent localized inflammation, lower genital tract infections, and high-risk genetic predispositions (Lynch and Cowden syndromes). Effective secondary prevention relies on elevating public awareness of AUB as an urgent diagnostic signal. Broadening access to outpatient diagnostic triage using transvaginal ultrasound and endometrial sampling enables prompt identification of precursor lesions while avoiding costly, invasive inpatient curettage. Mitigating the population burden of EC requires integrating metabolic health management into primary care, establishing risk-stratified clinical pathways, and integration of cascade genetic testing for families at high risk of hereditary cancer syndromes (such as Lynch and Cowden syndromes). Ultimately, establishing a unified national registry for endometrial precursor lesions will enable reliable prospective patient surveillance, mitigate regional disparities in access to specialized care, and minimize the rate of hyperplastic transformation into overt malignancy.

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Purpose. The aim of this paper is to evaluate endometrial hyperplastic disorders as an actionable precursor to EC from a public health perspective, analyzing risk determinants, early detection triage mechanisms, and population-based prevention strategies.

Material and Methods. We employed general scientific methodologies, including comprehensive literature search, analytical review, synthesis, and generalization. Relevant studies were retrieved from the PubMed and Google Scholar electronic databases using terms *"endometrial cancer"*, *"endometrial hyperplasia"*, *"epidemiology"*, *"abnormal uterine bleeding", "risk factors"*, *"early detection", "screening" and "prevention"*.

Results. EH constitutes a spectrum of abnormal endometrial proliferative changes ranging from benign glandular overgrowth to precancerous lesions, among which atypical EH/EIN represents an actionable pre-malignant phase along the continuum toward EC. Effective secondary prevention relies on elevating public awareness of AUB as an urgent diagnostic signal. Broadening access to outpatient diagnostic triage using transvaginal ultrasound and endometrial sampling enables prompt identification of precursor lesions while avoiding costly, invasive inpatient curettage. Mitigating the population burden of EC requires integrating metabolic health management into primary care, establishing risk-stratified clinical pathways, and integration of cascade genetic testing for families at high risk of hereditary cancer syndromes.

Conclusions. Atypical EH/EIN is a critical, actionable target for secondary prevention of endometrial cancer. Effectively mitigating population disease burden requires embedding metabolic risk management into primary care, expanding outpatient diagnostic triage for AUB, and establishing national precursor registries alongside cascade genetic testing to address healthcare disparities.

Key words: endometrial cancer, endometrial hyperplasia, epidemiology, population risk determinants, prevention, early detection triage, disease surveillance.

Рак ендометрію (РЕ) є найбільш поширеним злоякісним новоутворенням серед гінекологічних онкологічних захворювань, що визначає його як вагому проблему громадського здоров'я.

Мета – оцінити гіперпластичні процеси ендометрію як клінічно керований передраковий стан з позиції громадського здоров'я, проаналізувавши детермінанти ризику, шляхи для раннього виявлення та популяційні стратегії профілактики.

Матеріали і методи. У цьому дослідженні були застосовані загальнонаукові методологічні підходи, включно з комплексним пошуком літератури, аналітичним оглядом, синтезом та узагальненням отриманих даних. Пошук літературних джерел здійснювався у міжнародних наукових базах даних PubMed та Google Scholar із використанням ключових термінів: «рак

ендометрію», «гіперплазія ендометрію», «епідеміологія», «аномальна маткова кровотеча», «фактори ризику», «рання діагностика», «скринінг» та «профілактика».

Результати. ГЕ, що охоплює спектр патологічних проліферативних змін слизової оболонки матки – від доброякісного залозистого розростання до уражень із високим злоякісним потенціалом (атипова ГЕ/ендометріальна інтраепітеліальна неоплазія (ЕІН)), є клінічно керованою передраковою фазою в континуумі прогресування до РЕ. Прогресування захворювання зумовлене переважно неопонованою естрогенною стимуляцією ендометрію, яка тісно пов'язана з ожирінням та метаболічним синдромом. Цей естрогенний стимул додатково посилюється хронічною стресовою сигналізацією за віссю «гіпоталамус – гіпофіз – надниркові залози», персистуючим локальним запаленням, інфекціями нижніх відділів статевих шляхів і генетичною схильністю. Ефективна вторинна профілактика ґрунтується на підвищенні обізнаності населення щодо аномальних маткових кровотеч як ургентного діагностичного симптому ГЕ. Розширення доступу до медичної допомоги на амбулаторному етапі з використанням трансвагінального ультразвукового дослідження та біопсії ендометрію забезпечує своєчасне виявлення передракових змін, дозволяючи уникнути високовартісного й інвазивного вишкрібання порожнини матки у стаціонарних умовах. Виявлення популяційних детермінант ризику та їх зниження вимагає інтеграції менеджменту метаболічного здоров'я в первинну ланку медичної допомоги (контроль маси тіла, регулярна фізична активність, скринінг інсулінорезистентності та гіперглікемії), впровадження стратифікованих за ризиком клінічних маршрутів та застосування каскадного генетичного тестування для родин із високим спадковим ризиком синдромів Лінча та Коудена. У підсумку, створення єдиного національного реєстру передракових станів ендометрію забезпечить надійний проспективний нагляд за пацієнтками, нівелює регіональні диспаритети щодо доступу до спеціалізованої медичної допомоги та мінімізує частоту трансформації гіперплазії ендометрію в маніфестний злоякісний процес.

Висновки. Атипова ГЕ/ЕІН є критичною клінічно керованою мішенню для вторинної профілактики раку ендометрію. Виявлення популяційних детермінант ризику та їх зниження вимагає інтеграції менеджменту метаболічного здоров'я в первинну ланку медичної допомоги, розширення доступу до ранньої діагностики ГЕ на амбулаторному етапі за допомогою трансвагінального ультразвукового дослідження та біопсії ендометрію у пацієнток з АМК, а також створення національних реєстрів передракових станів ендометрію поряд із каскадним генетичним тестуванням для подолання диспаритетів у сфері охорони здоров'я.

Ключові слова: рак ендометрію, гіперплазія ендометрію, епідеміологія, популяційні детермінанти ризику, профілактика, раннє виявлення, епідеміологічний нагляд.

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