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Review

Immunoinflammatory and Metabolic Drivers of Endometrial Hyperplasia: From Unopposed Estrogen to Precision Medicine

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Abstract: Endometrial hyperplasia (EH) is a precursor to carcinoma, with the risk amplified by obesity, polycystic ovary syndrome, insulin resistance, and delayed childbearing through estrogen excess and anovulatory "unopposed estrogen" states. This review synthesizes endocrine, metabolic, molecular, diagnostic, and therapeutic evidence in EH, distinguishing findings from unvalidated mechanisms to inform biomarker development without displacing histopathology. The literature was searched in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar (January 2000–March 2026; 2020 onward) using terms spanning EH/Endometrial intraepithelial neoplasia, cytokines, oxidative stress, PI3K/AKT/mTOR, obesity, microbiome, and biomarkers; English-language studies, reviews, meta-analyses, and guidelines were weighted toward human EH data, guided by the Scale, without a formal risk-of-bias tool. Evidence supports endocrine driving: estrogen receptor signaling promotes proliferation via cyclins and PI3K/AKT and MAPK pathways, whereas progesterone loss facilitates persistence. EH shows elevated interleukin-6 (IL-6), TNF-α, IL-1β, and IL-8, engaging NF-κB/STAT3 circuits, although limited. Oxidative stress may affect progression through reactive oxygen species-driven peroxidation and DNA (Deoxyribonucleic Acid) damage. Recurrent alterations (PTEN loss; PIK3CA, KRAS, and β-catenin changes) inform the stratification and therapy resistance in atypical EH/Endometrial intraepithelial neoplasia. Histopathology remains central, with immunohistochemistry. Clinically, levonorgestrel-releasing intrauterine system shows superior regression compared to progestins, and metformin is adjunctive. The rate of occult carcinoma at hysterectomy was 45.3%. Fertility-sparing levonorgestrel-releasing intrauterine system is effective but carries a risk of disease progression/recurrence. Overall, EH is hormone-driven and involves metabolic, inflammatory, oxidative, and molecular modifiers. Precision care requires the prospective validation of biomarker panels beyond histology and clinical risk.

Keywords: Endometrial Hyperplasia; Estrogen; Progesterone; Inflammation; Cytokines

1. Introduction

Endometrial hyperplasia (EH) is a significant gynecological condition characterized by abnormal endometrial gland growth due to prolonged exposure to estrogen. It is prevalent, appearing in 15–40% of gynecological cases, especially among women with metabolic and reproductive issues [1]. EH is clinically important as a precursor to endometrial carcinoma, with atypical forms posing a high risk of malignancy [2–4]. Studies have shown that EH often coexists with or progresses to cancer, stressing the need for monitoring and treatment. Its epidemiological

significance grows with rising obesity, polycystic ovary syndrome (PCOS), and delayed childbearing, which increase estrogen excess and anovulatory conditions, elevating the risk of EH [1,2]. Data from the PCOS group showed significant EH and cancer rates, necessitating endometrial evaluation in high-risk women [5]. Population data suggest that rising obesity contributes to the incidence of endometrial neoplasia, including EH and cancer [6]. EH should be considered a global health issue with oncological implications [1,4].

EH results from an estrogen-progesterone imbalance with prolonged estrogen exposure and inadequate progesterone. Progesterone curbs the effects of estrogen by limiting epithelial growth and promoting differentiation; without it, proliferation continues, preventing regular shedding [2].

This is the "unopposed estrogen" theory: estrogen drives mitogenesis, whereas progesterone restrains growth. Low or absent progesterone levels intensify proliferation, promoting hyperplasia [2,7]. Research has shown that progesterone significantly inhibits estrogen-induced proliferation, highlighting its antiproliferative role [7,8].

Hormonal imbalance occurs in scenarios such as chronic anovulation, where a lack of ovulatory progesterone leaves the endometrium exposed to estrogen [2,9]; unopposed hormone therapy, where estrogen increases the risk of hyperplasia [2,10]; and tamoxifen exposure, which stimulates endometrial growth despite antiestrogenic breast effects [2,11].

This environment encourages epithelial proliferation, disrupts cell cycle regulation, and promotes glandular expansion. Progesterone inhibits pathways such as Wnt/β-catenin; without it, these pathways remain active, aiding hyperplasia-carcinoma progression [7,12]. Thus, EH is the result of continuous estrogen stimulation without progesterone opposition [2].

The conventional endocrine framework attributes EH to prolonged estrogen exposure without sufficient progesterone. The findings suggest that inflammatory and metabolic irregularities may influence this process, especially in women with obesity, insulin resistance, or polycystic ovary syndrome [13–15]. Although cytokines, chemokines, and prostaglandins may affect proliferation, repair, and progression, evidence shows associations and does not establish inflammation as the cause of EH [13,14,16]. EH remains hormone-driven but is modified by immune and metabolic factors.

Proinflammatory agents include IL-6, TNF-α, IL-1β, and IL-8, which may activate the NF-κB and STAT3 pathways [17–21]. However, the evidence comes largely from studies on cancer, endometriosis, or experimental models; therefore, extrapolation to EH requires caution. Prospective evidence for causation of EH is lacking. Overall, EH may involve unopposed estrogen, metabolic dysfunction, inflammatory signaling, and defective apoptotic regulation; however, the contribution and causal relationships of each factor remain unclear.

Oxidative stress is a potential link between chronic inflammation and the development of tissue damage. Reactive oxygen species (ROS) can trigger lipid peroxidation, forming malondialdehyde and 4-hydroxynonenal, which disrupt cellular membranes, proteins, and DNA [22,23]. Research on other cell types indicates that cytoskeletal integrity and plasma membrane repair are crucial for cell survival and mechanotransduction after injury [24,25]. However, these findings provide biological context across tissues and not direct evidence of EH.

ROS can activate stress-responsive pathways, such as NF-κB, and inflammatory mediators can enhance ROS production [26]. Ongoing oxidative damage may hinder DNA repair or increase replication stress [27,28]. Nevertheless, direct longitudinal evidence linking oxidative biomarkers in endometrial tissue to the progression from EH to carcinoma is limited.

Therefore, oxidative stress should be viewed as a potential modifier of EH biology, rather than a confirmed cause of neoplastic progression. The literature on ferroptosis supports the association between ROS and lipid damage but does not independently establish abnormal survival or malignant progression in the endometrial tissue [29].

Endocrine stimulation, inflammatory mediators, redox injury, and PTEN/PIK3CA-driven PI3K/AKT/mTOR signaling may converge, but prospective validation is required [30,31].

Obesity can alter the endocrine and immune environments through estrogen production, adipokine imbalance, and low-grade inflammation [32,33]. Adipose studies have shown that macrophage remodeling and inflammatory mechanisms contribute to insulin resistance [34–36]; however, they provide indirect evidence for EH and do not demonstrate the causality of endometrial macrophages.

Insulin resistance may drive proliferation through insulin and insulin-like growth factor signaling, whereas TNF-α and IL-6 can impair insulin signaling [32]. The studies by Lee et al. and Liao et al. [35,36] offer context, but endometrial-specific studies and clinical outcome data should be prioritized.

Overall, obesity and insulin resistance are risk factors for endocrine, inflammatory, and growth factor signal interactions. The strongest evidence is their epidemiological association with endometrial neoplasia; however, the immune pathways mediating EH persistence remain poorly defined [33,37].

Conventional management relies on histologic classification, progestin treatment with endometrial surveillance, and hysterectomy for EIN/atypical EH when necessary [38]. Immune markers have not been validated for routine decision-making. A translational approach would confirm histology, document metabolic risk factors, and use molecular or inflammatory tests only in research or specialist settings with thresholds and outcome-linked validations.

This review examines the interactions among endocrine, metabolic, inflammatory, oxidative, and molecular findings in EH, distinguishing well-established evidence from theoretical mechanisms. It targets gynecologists, pathologists, and translational researchers exploring how biomarkers can enhance, not replace, guideline-based histopathology and care. This review consolidates the evidence, identifies knowledge gaps, and suggests approaches for biomarker validation and precision treatment.

2. Methods

This review integrates endocrine, immuno-inflammatory, molecular, metabolic, diagnostic, and therapeutic evidence of EH. Reporting and evaluation were guided by the Scale for the Assessment of Narrative Review. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews guidelines were not utilized as this study was a narrative, not a scoping, review.

A search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for literature from January 2000 to March 2026, focusing on studies published from 2020 onwards. The search terms included "endometrial hyperplasia," "endometrial intraepithelial neoplasia," inflammation, cytokines, oxidative stress, PTEN, PI3K/AKT/mTOR, obesity, insulin resistance, microbiome, biomarkers, progestins, metformin, and immunomodulation. References from reviews and guidelines were scrutinized.

The review considered English-language research, systematic reviews, meta-analyses, and guidelines addressing EH or endometrial precursor biology, including insights, excluding non-peer-reviewed materials, sources lacking details, and articles without mechanistic or clinical relevance.

The titles and abstracts underwent initial relevance screening, followed by full-text evaluation. Data were qualitatively charted according to study design, population or model, tissue context, biomarkers or pathways, treatment, and clinical outcomes. Because the review was conceived as a narrative synthesis, no numerical screening log was maintained, and retrospective counts were fabricated. **Figure 1** illustrates the selection process without numerical data.

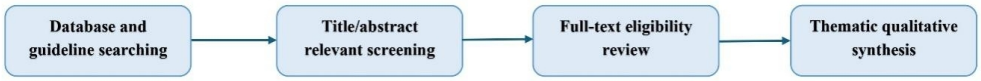

Figure 1. Simplified workflow for literature identification, screening, eligibility, assessment, and narrative synthesis.

The evidence was categorized into endocrine drivers, immuno-inflammatory signaling, oxidative stress, molecular changes, metabolic interactions, immune microenvironment, diagnostic biomarkers, and treatment outcomes. The greatest weight was given to direct human EH evidence, followed by endometrial cancer or other gynecological studies, animal models, and cross-tissue mechanistic research.

No risk-of-bias tool was applied, which affected certainty. Conflicting results were prioritized based on EH evidence, prospective designs, samples, assays, consistency, and outcomes. Inconsistent evidence was preserved, and the conclusions were classified as associative, plausible, or investigational. Ethical approval and consent were not required because the data were analyzed.

3. Cytokine Dysregulation

EH involves chronic low-grade inflammation, with elevated IL-6, TNF-α, IL-8, and IL-1β levels, creating a pro-growth environment. These cytokines target the NF-κB and STAT3 pathways, enhancing inflammatory gene expression, advancing the cell cycle, and inhibiting apoptosis, thus promoting continuous growth instead of normal

resolution [39]. EH should be viewed as inflammation-driven, not just hormonal imbalance. IL-6 is crucial and is produced by endometrial stromal cells when exposed to inflammatory triggers and influenced by estrogen, showing an endocrine-immune interaction [40]. IL-6 maintains STAT3 activation, whereas NF-κB enhances IL-6 expression, forming a feedback loop that stabilizes inflammatory signaling [41]. Clinically, IL-6 is linked to stromal expansion, angiogenic support, and remodeling, making it a potential biomarker for risk and a target for research [42]. Cytokine dysregulation supports the view of EH as an immune-active lesion, where inflammation influences tissue behavior and outcomes (**Table 1**). This perspective supports biomarker-guided monitoring and therapeutic approaches that combine hormonal regulation with immune modulation.

Table 1. Immune-inflammatory mediators in EH.

Mediator	Source	Key Pathways Activated	Biological Effects	Clinical Relevance
IL-6	Stromal cells, macrophages, adipocytes	STAT3, NF-κB	Promotes proliferation, angiogenesis, inhibits apoptosis	Biomarker for progression risk
TNF-α	Macrophages, adipose tissue	NF-κB, MAPK	Induces cytokine cascade, inflammation amplification	Associated with metabolic inflammation
IL-1β	Immune cells	NF-κB	Enhances inflammatory signaling, cytokine production	Associated with disease persistence
IL-8	Stromal cells, epithelial cells	NF-κB	Chemotaxis, angiogenesis, anti-apoptotic effects	Correlates with active disease
IL-17	T helper cells	NF-κB	Sustains chronic inflammation	Contributes to immune dysregulation

Note: IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-alpha; IL-1β = Interleukin-1 beta; IL-8 = Interleukin-8; IL-17 = Interleukin-17; STAT3 = Signal Transducer and Activator of Transcription 3; NF-κB = Nuclear factor kappa B; MAPK = Mitogen-activated protein kinases.

4. Hormonal Drivers and Proliferative Signaling

EH arises from prolonged exposure to estrogen without adequate progesterone, known as unopposed estrogen, which removes the usual endometrial growth control [2]. Progesterone counterbalances estrogen by limiting epithelial growth and promoting differentiation; its absence or ineffectiveness leads to ongoing proliferative activity, keeping the endometrium highly responsive [43].

Estrogen receptor activation directly promotes cell proliferation. Estrogen signaling stimulates endometrial cell growth, increases cell cycle regulators such as cyclin D1 and E, and triggers pathways such as PI3K/AKT and MAPK, supporting survival and tissue expansion [44,45]. Non-classical estrogen signaling through G-protein-coupled estrogen receptor also activates the PI3K and MAPK pathways, enhancing proliferation and reinforcing estrogenic effects [46].

Progesterone loss diminishes a crucial antiproliferative checkpoint. Reduced progesterone receptor signaling is linked to decreased responsiveness and a phenotype aligned with unopposed estrogen, while progesterone may also suppress PI3K/Akt-related resistance mechanisms [47]. Studies have shown that progesterone significantly inhibits estrogen-induced proliferation and restores secretory maturation, confirming its role in limiting endometrial growth [43].

The most recognized framework for this phenomenon is hormonal imbalance. Although the PI3K/AKT and MAPK signaling pathways and inflammatory mediators may influence lesion persistence or advancement, evidence does not support inflammation as the primary cause.

5. Immuno-Inflammatory Findings

EH might show IL-6, TNF-α, IL-1β, and IL-8 mediating stromal–epithelial communication [42,47]. Evidence is scarce, and insights from endometrial cancer, endometriosis, or non-endometrial models are supportive, not causal. NF-κB and STAT3 converge inflammation and survival: cytokine signaling may promote proliferation, survival, angiogenesis, and matrix remodeling, while endocrine stimulation influences the network [42,48–50]. Inflammation may affect lesions; however, the intensity, timing, and direction remain unclear. Prospective studies linking cytokine profiles with regression, recurrence, and progression are needed before application [51,52].

6. Oxidative Stress and Tissue Damage

Oxidative stress is a secondary mechanism of endometrial damage, characterized by increased reactive oxygen species (ROS) and lipid peroxidation. This leads to the formation of reactive aldehydes, such as malondialdehyde

(MDA), indicating membrane lipid damage and interference with cellular signaling [53]. Inflammation and tissue injury often show elevated MDA levels, oxidative biomarkers, and structural harm, suggesting that redox imbalance drives lesion advancement [54]. The impairment of the antioxidant system is crucial. When defenses such as superoxide dismutase, catalase, and glutathione are reduced, cells cannot neutralize excess ROS or restore redox balance [54,55]. This allows oxidative damage to persist, worsening tissue dysfunction and inflammation. Oxidative stress also facilitates DNA damage, oxidizes DNA bases, causes strand damage, hinders repair, and increases mutation risk and genomic instability [56,57] (**Table 2**). Lipid peroxidation products form DNA adducts and lesions prone to mutation; repair may be slow at hotspots, increasing the risk of genetic damage [57,58]. Thus, oxidative stress links chronic inflammation and genetic instability, explaining why prolonged inflammatory injury can progress to atypia or neoplasia [53,56].

Table 2. Oxidative stress and redox imbalance in EH.

Factor	Mechanism	Cellular Impact	Clinical Implication
Reactive oxygen species	Generated during inflammation	DNA damage, lipid peroxidation	Promotes mutation and progression
Malondialdehyde	Lipid peroxidation product	Membrane damage, protein modification	Marker of oxidative stress
Antioxidant enzymes (SOD, Catalase, GSH)	Detoxification pathways	Reduced activity and oxidative imbalance	Indicates impaired defense system
Lipid peroxidation products	Oxidative degradation of lipids	DNA adduct formation, mutagenesis	Links inflammation to carcinogenesis

Note: SOD = Superoxide dismutase; GSH = Glutathione.

7. Molecular and Genetic Alterations

A significant molecular event in endometrial hyperplasia and the associated endometrioid neoplastic sequence is PTEN loss, which affects PI3K/AKT signaling. PTEN mutations are prevalent in precursor lesions and are common in endometrioid carcinoma, highlighting their role in malignant progression [59]. In large endometrioid cohorts, PTEN loss is a molecular marker with prognostic value in subgroups, emphasizing its importance in outcome evaluation [60].

Alterations in PIK3CA, KRAS, and β-catenin/Catenin Beta-1 also contribute to the disease progression. PIK3CA mutations are more frequent in carcinoma than in atypical hyperplasia, linking them to invasion [59]. KRAS mutations occur in a parallel pathway and may act with other PI3K-pathway abnormalities [61]. β-catenin abnormalities are associated with an advanced neoplastic phenotype involving the Wnt pathway in lesions closer to the endometrial intraepithelial neoplasia (EIN) and carcinoma.

These alterations increase proliferation and decrease apoptosis in the cells. PTEN loss activates the PI3K/AKT/mTOR signaling, while PI3K-pathway mutations amplify growth signaling [62]. In endometrioid cell models, tumors with PIK3CA and PTEN mutations depend on PI3K/mTOR inhibition, and KRAS-mutant cells show a limited response to MEK inhibition, indicating a predisposition to survival and proliferation [63]. PTEN deficiency can initiate additional oncogenic signaling pathways, enhancing the tumorigenic potential [64] (**Table 3**).

Table 3. Molecular and genetic alterations in EH.

Gene/Marker	Pathway	Mechanism of Action	Clinical Significance	Therapeutic Implication
PTEN	PI3K/AKT/mTOR	Tumor suppressor loss and increased proliferation	Early event in EH and carcinoma	Target for pathway inhibition
PIK3CA	PI3K/AKT	Activating mutation and enhanced growth signaling	Associated with progression	Predicts therapy resistance
KRAS	MAPK	Constitutive activation and proliferation	Linked to aggressive phenotype	Limited response to targeted therapy
CTNNB1 (β-catenin)	Wnt pathway	Alters cell adhesion and signaling	Indicates advanced lesions	Potential therapeutic target
p53	Tumor suppressor	Mutation and genomic instability	Associated with high-risk disease	Guides risk stratification

Note: PTEN = Phosphatase and Tensin Homolog; PIK3CA = Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit; KRAS = Kirsten rat sarcoma viral oncogene homolog; CTNNB1 = Catenin β; p53 = Tumor protein p53; PI3K = Phosphoinositide 3-kinase; AKT = Protein Kinase B/PKB; mTOR = mammalian Target of Rapamycin; MAPK = Mitogen-activated protein kinases.

These mutations affect therapeutic resistance. PTEN-mutant endometrioid tumors may have altered sensitivity to pathway-targeted agents, requiring combination approaches rather than single-agent PI3Kβ inhibition [63]. Clinically, PTEN mutations are linked to a less favorable response to fertility-preserving treatment in young pa-

tients with atypical hyperplasia and endometrioid cancer, suggesting reduced responsiveness to conservative therapy [59]. This finding supports the perspective that pathway alterations affect treatment durability and resistance patterns.

Importantly, these alterations increase the risk of malignancy, identifying lesions closer to invasive behavior. PIK3CA mutations are rare in hyperplasia without atypia but are common in carcinoma, indicating invasion. PTEN mutations appear at the precursor stage and become entrenched in the malignant pathway, whereas KRAS and Catenin Beta-1 abnormalities indicate progression. Collectively, these mutations define lesions with greater malignant potential than morphologically similar but genomically quieter hyperplastic lesions.

Overall, molecular profiling enhances risk stratification by distinguishing indolent lesions from those with active oncogenic signaling, invasion-associated mutations, and reduced treatment responsiveness. Integrated profiling of PTEN, PIK3CA, KRAS, and related pathway lesions can help identify patients at a higher risk of progression and guide individualized management [59].

8. Metabolic and Endocrine-Immune Interactions

Obesity and insulin resistance can affect the success of fertility-preserving treatments through endocrine, metabolic, and molecular mechanisms. PTEN mutations and insulin resistance have been linked to poorer outcomes in conservative treatment for atypical hyperplasia and endometrioid cancer [59]. Adipose tissue inflammation offers an explanation [32–36], but direct endometrial evidence is lacking. Mismatch repair deficiency is pertinent to atypical EH/EIN and may help assess hereditary cancer risk [65].

9. Endometrial Microenvironment and Immune Cells

The endometrial microenvironment in hyperplasia maintains a chronic proliferative state through interactions between the immune and stromal compartments. Communication between these cells orchestrates tissue repair, inflammation, and remodeling; however, dysregulation can lead to sustained growth and an immunosuppressive environment [66].

Macrophages regulate this microenvironment. Changes in macrophage number and polarization are linked to disease progression, promoting growth, immune evasion, and matrix remodeling [67]. In endometrial cancer datasets tracking hyperplasia to malignancy, immune infiltration signatures reveal macrophage-related changes, indicating dynamic myeloid remodeling [68]. These cells contribute to cytokine amplification and create a microenvironment conducive to proliferation and invasion [4].

Neutrophil counts increase in the advanced stages of the disease. In obese pre-malignant endometrium, neutrophils increase in tumor glands compared to endometrial cancer, suggesting recruitment during disease progression and local inflammation. Neutrophils release proteases, reactive mediators, and cytokines, reinforcing tissue injury signals and remodeling the extracellular matrix [69].

Endometrial stromal cells actively produce inflammatory mediators. They secrete IL-6 in response to IL-1, TNF, and IFN-γ, modulated by estradiol [70]. Stromal-epithelial interactions are associated with IL-6/STAT3 signaling, enhancing proliferative signaling. Thus, stromal cells respond to inflammation and amplify the cytokine-driven growth.

Immune infiltration characterizes EH and its progression states, including macrophages, neutrophils, CD8+ T cells, regulatory T cells, and dendritic cells [71]. In endometrial lesions, immune infiltration is linked to altered cytokine landscapes and immune tolerance, indicating immunological activity [68]. This aligns with the notion that the endometrial immune landscape can predict clinical behavior [71].

Immune and stromal cells support EH through cytokine-rich network. Key mediators include IL-6, TNF-α, IL-1β, and IL-8, which activate NF-κB and STAT3, driving proliferation, survival, and resistance to growth control. IL-6 is significant as stromal cells produce it in response to inflammation, which is modulated by estrogen, linking endocrine and immune regulation [70]. These signals promote angiogenesis, stromal expansion, and matrix turnover, thereby supporting tissue remodeling and creating a proliferative niche.

10. Microbiome and Epigenetics

The endometrial microenvironment in hyperplasia sustains chronic proliferation through immune and stromal cell interaction. These communications coordinate tissue repair, inflammation, and remodeling; when dysreg-

ulated, they cause continuous growth and immunosuppression [72]. Reviews suggest that microbiome dysbiosis and the gut–endometrium axis promote systemic inflammation, hormonal disturbances, and local immune changes in the endometrium [72,73]. A narrative review highlighted that endometrial microbiome changes might influence immune modulation and pro-tumorigenic signaling, although further validation is needed [72]. A study on chronic endometritis and endometrial polyps showed altered uterine tract microbiota compared to that in controls [74]. Aberrant DNA methylation is a factor in endometrial carcinogenesis, with promoter hypermethylation of Human MutL homolog 1, Adenomatous Polyposis Coli, and E-cadherin in endometrial cancer and atypical hyperplasia [75]. Genome-wide profiling has shown that tumor tissue has a distinct methylation pattern from the normal endometrium, indicating early epigenetic changes during progression [76]. Non-invasive biomarkers are supported by urine-based methylation detection of endometrial cancer using Growth Hormone Secretagogue Receptor, Somatostatin, and Zic Family Zinc Finger 1 genes [77]. A systematic review identified 313 miRNAs associated with endometrial cancer, including miRNA expression and methylation alterations [78]. This supports the discussion of miRNA dysregulation as part of the epigenetic landscape. Broader epigenetic literature indicates that DNA methylation and miRNA networks influence inflammatory signaling and immune responses [79]. This supports the notion that microbiome shifts and epigenetic changes may converge on cytokine pathways, immune surveillance, and chronic inflammation in the endometrial microenvironment.

11. Diagnostic and Biomarker Findings

Histopathology remains crucial for diagnosis. An endometrial biopsy or curettage assesses glandular density, structural complexity, and cytological atypia, with the EIN/benign hyperplasia framework preferred for its reproducibility and risk association. Pipelle sampling is also accurate for detecting endometrial cancer and atypical hyperplasia [80].

IHC improves diagnosis and risk assessment (**Table 4**):

- PTEN: In endometrial neoplasia, PTEN loss or decrease is an early event. In carcinoma biopsies, PTEN immunohistochemistry and next-generation sequencing complement the detection of PTEN anomalies [81]. However, PTEN immunohistochemistry alone lacks validation as a diagnostic or prognostic tool for EH.
- Ki-67: Ki-67 indicates proliferation, but no standard thresholds or outcome-related performance in EH have been established. Consequently, it should be considered an investigational tool, not a replacement for histopathologic classification.
- p53: Abnormal p53 staining can identify endometrial lesions; however, its utility in EH evaluation remains limited. Interpretation should combine morphological analysis with molecular assessment when necessary and not be used alone.
- IL-6: IL-6 indicates inflammatory signaling and estrogen-immune interactions in endometrial cancer models [20]. However, no direct evidence defines an IL-6 threshold for predicting whether EH will regress or progress, and its application in EH remains under investigation.

Table 4. Diagnostic biomarkers and tools.

Tool/Marker	Type	Function	Clinical Utility
Histopathology	Gold standard	Structural assessment	Diagnosis and classification
PTEN IHC	Molecular marker	Detects tumor suppressor loss	Risk stratification
Ki-67	Proliferation marker	Measures cell division rate	Indicates disease activity
p53	Tumor suppressor marker	Detects high-risk lesions	Identifies aggressive disease
IL-6	Inflammatory biomarker	Reflects immune activation	Predicts progression
NGS Panels	Genomic profiling	Detects mutations	Precision medicine application

Note: PTEN IHC = Phosphatase and Tensin Homolog Immunohistochemistry; Ki-67 = Antigen Kiel 67/MKI67; p53 = Tumor Protein p53; IL-6 = Interleukin-6.

PTEN loss is a key molecular risk marker for progression and an early event in tumorigenesis. It identifies high-risk lesions and potential malignancies [80]. The best approach is to integrate multiple markers. Histology defines lesions, while PTEN, Ki-67, p53, and IL-6 refine the behavior and risk. This approach enhances diagnostic confidence and captures structural and functional changes, and is valuable as lesions are driven by proliferative and inflammatory pathways [80,82].

12. Therapeutic Outcomes and Molecular Predictors

The levonorgestrel-releasing intrauterine system (LNG-IUS) is the most effective conservative treatment for endometrial hyperplasia and related premalignant conditions, showing higher regression and complete response rates than oral progestins (**Table 5**). It is also more effective in resolving early molecular abnormalities, such as Paired box gene 2- (PAX2) and PTEN-null glands, which are linked to therapeutic outcomes. This suggests that the superiority of the LNG-IUS stems from enhanced local progestin exposure and greater reversal of abnormal endometrial biology [83].

Table 5. Therapeutic strategies and outcomes.

Therapy	Mechanism of Action	Indications	Advantages	Limitations
LNG-IUS	Local progestin delivery	Non-atypical EH, fertility preservation	High efficacy, low systemic effects	Irregular bleeding, expulsion risk
Oral Progestins	Systemic hormonal therapy	EH without atypia	Widely available	Lower compliance, systemic effects
Metformin	Improves insulin sensitivity	Metabolic-associated EH	Reduces proliferation	Limited standalone efficacy
Hysterectomy	Surgical removal	Atypical EH/EIN	Definitive treatment	Loss of fertility
Combined therapy	Hormonal and metabolic	Resistant cases	Improved outcomes	Requires monitoring

Note: LNG-IUS = levonorgestrel-releasing intrauterine system; EH = Endometrial hyperplasia; EIN = Endometrial intraepithelial neoplasia.

Oral systemic progestins are valuable but less consistent and enduring than LNG-IUS, partly due to daily adherence requirements and systemic side effects. Some lesions respond better to local delivery than to systemic exposure. In atypical endometrial hyperplasia, oral progestins can induce remission, but response rates are generally lower than those with LNG-IUS, emphasizing the importance of the delivery method for treatment effectiveness. Metformin should be an adjunct, not a replacement, for progestin therapy, particularly for patients with obesity, insulin resistance, or metabolic syndrome, where it can help counter disease persistence or recurrence.

Treatment response depends on the therapy choice, lesion molecular profile, and patient metabolic context. Persistent PTEN and PAX2 abnormalities are linked to poorer responses, whereas their clearance is associated with better outcomes [83]. Long-term follow-up shows a relapse risk post-treatment, highlighting the need for ongoing surveillance and individualized management. Evidence supports a nuanced view of conservative therapy: the best outcomes arise when histology, molecular features, and metabolic status are considered together [83,84].

13. Conservative Versus and Surgical Management

In endometrial intraepithelial neoplasia (EIN) and early endometrioid conditions, balancing cancer control and fertility preservation is crucial. The standard treatment is surgical, usually a hysterectomy with staging, to remove premalignant or malignant tissue and eliminate the risk of uterine cancer. This is vital for EIN, where hidden carcinoma often appears during hysterectomy; one study found carcinoma in 45.3% of EIN patients, highlighting the importance of surgical-pathologic evaluation over observation [85]. Conversely, conservative management is for patients desiring fertility or those who are unsuitable for surgery. Progestin-based treatments, especially LNG-IUS, can induce remission but do not eliminate cancer risk, requiring ongoing biopsies, imaging, and counseling about recurrence and progression [86].

Conservative management of patients with EIN/AEH can achieve high short-term success; however, recurrence remains an issue. LNG-IUS treatment for atypical hyperplasia and early-stage cancer shows regression rates in the upper 80% for atypical hyperplasia, although some patients may experience disease progression during treatment [86]. Molecular and biological diversity also affect the results; PTEN mutations and insulin resistance are linked to less favorable outcomes in fertility-preserving treatments, indicating that EIN is not uniform [59]. Research shows that conservative therapy succeeds when the disease has a favorable molecular and clinical profile, while adverse metabolic factors and molecular abnormalities increase the risk of treatment failure or recurrence [59].

Fertility-preserving therapies, especially those involving the use of LNG-IUS, can be successful when patients are carefully selected and monitored. A study on atypical complex hyperplasia and endometrial cancer treated with LNG-IUS showed a complete response in 89.3% of atypical hyperplasia cases and 81.3% of grade 1 endometrial cancer cases. Among those attempting pregnancy, 73.7% succeeded [86]. Prognosis is clarified by molecular subtype: tumors with p53 abnormalities have the worst response and highest recurrence, while DNA polymerase epsilon, catalytic subunit (POLE) mutations have the best outcomes, with complete response in one cohort [87]. PTEN mu-

tations are linked to poor fertility-preserving outcomes, and insulin resistance worsens the response, highlighting the need to integrate oncologic evaluation with metabolic and molecular risk assessment [59].

In counseling, it is crucial to include disease progression and recurrence risks, as conservative management controls but does not eliminate the disease. In the LNG-IUS group, progressive disease occurred in 3.6% of patients with atypical hyperplasia, 12.5% with grade 1 cancers, and 25.0% with grade 2 cancers, showing that "fertility-sparing" treatments have a significant failure risk [86]. Recurrence after remission is frequent; therefore, maintenance therapy is considered necessary. A multicenter study showed that it reduced recurrence but lowered pregnancy and live birth rates, highlighting the balance between oncological safety and fertility objectives [88]. While re-treatment can be effective, relapse may occur, suggesting that fertility preservation is temporary as the predisposition remains [89]. Variability is partly explained by molecular subtypes: p53-abnormal disease has the least favorable outcomes, POLE-mutated disease is more responsive, and PTEN-mutant disease is linked to poorer fertility-preserving results [59,87].

Hysterectomy is the most reliable surgical option for oncologic outcomes, as it eliminates the lesion and recurrence potential. It is preferred when fertility preservation is not a concern or when conservative treatment fails [85]. Patients who choose conservative therapy can still achieve significant reproductive outcomes. In an LNG-IUS cohort study, many patients in remission succeeded in conceiving, including those with assisted reproductive technologies [86]. A recent follow-up reported a pregnancy rate of 58.24% and a live birth rate of 48.65%, with higher rates in the *in vitro* fertilization and embryo transfer and ovulation induction groups. Obstetric complications include threatened abortion, cervical insufficiency, and placenta accreta/increta [90]. Fertility preservation requires cancer monitoring before conception and high-risk obstetric care after conception.

The evidence supports a tiered approach: surgery is optimal when fertility preservation is not a priority, while conservative management is suitable for selected EIN/Atypical Endometrial Hyperplasia or early endometrioid cases with diligent follow-up [85,86]. LNG-IUS and progestin-based therapies can achieve high complete response rates, but the risks of recurrence, progression, and eventual hysterectomy remain [85,88]. Molecular subtype and metabolic status enhance risk stratification, with PTEN mutation, insulin resistance, and p53-abnormal disease linked to poorer outcomes, while POLE-mutated disease shows the best responses [59,87]. Conservative management should be considered a temporary, closely monitored strategy for childbearing and not a cure [85,88].

14. Integrated Endocrine and Metabolic Implications

Obesity, insulin resistance, and progesterone resistance can amplify estrogenic and growth factor signaling, affecting the outcomes of conservative therapy [59,88,91]. These links support the inclusion of metabolic assessment in evaluations, although treatments targeting PI3K/AKT or anti-inflammatory pathways remain under investigation. The cytokine and NF-κB/STAT3 mechanisms are detailed in the immuno-inflammatory section and are not reiterated. Current evidence does not support the use of cytokine-targeted therapies outside clinical trials.

ROS-mediated injury may intersect with AKT/mTOR survival pathways and genomic instability [27–31]. Studies involving Sptbn1 and Prkd1 across tissues highlight the role of membrane integrity and repair in survival [24,25], although their relevance to EH remains theoretical and requires validation in endometrial contexts.

EH is best represented as a hormone-driven lesion influenced by metabolic conditions, inflammatory signaling, and molecular changes. This model is a framework for generating hypotheses rather than confirming singular pathways. Metabolic and molecular irregularities may affect persistence, recurrence, and progression. Consequently, treatment decisions should be based on histology and clinical risk, with molecular and immune markers being assessed in prospective studies.

15. Limitations

The limitations of this review stem from the diverse source designs, populations, tissue contexts, assays, and outcome definitions. Neither a formal risk-of-bias tool nor a prospective screening log was used in this review. Much of the mechanistic literature is based on endometrial cancer, endometriosis, animal models, or non-endometrial tissues; these sources lend plausibility but do not confirm causality in EH. Publication and language biases are possible, and many biomarkers lack validated thresholds or proven incremental utility. Therefore, recommendations for therapies and biomarkers should be viewed as research priorities, not standard care.

16. Recommendations

Standardization of tissue collection, histological classification, biomarker testing, and outcome measurement is necessary. Prospective studies should determine whether predefined panels add predictive value to histological and clinical factors. Clinicians should assess obesity, diabetes, and insulin resistance, follow guidelines for progestin or surgical management, and monitor responses through scheduled endometrial sampling. Metformin may be considered for patients with metabolic needs, whereas anti-inflammatory or pathway-specific therapies should remain in clinical trials. Safety monitoring is essential for combination treatments, as antidiabetics, steroids, and other drug categories can affect tissue remodeling, requiring integrated biomarkers, imaging, and histological analysis.

17. Future Directions

Future research should focus on prospective multicenter cohorts and intervention studies to clarify the association versus causation. Candidate markers, including tissue cytokines, oxidative stress indicators, PTEN/PI3K changes, mismatch repair status, and metabolic measures, should be evaluated using predetermined clinically significant thresholds and outcomes. Trials targeting IL-6/STAT3, NF-κB, antioxidants, or other strategies require robust preclinical evidence and safety evaluations before clinical use. Microbiome and multi-omics studies should include contamination controls, external validation and reporting. Prediction models should be compared with clinical and histological models and independently validated before application.

18. Conclusions

EH is a hormone-influenced precursor lesion, with its behavior altered by metabolism, inflammatory signals, oxidative damage, and molecular alterations. Although research indicates links between these factors, it does not confirm inflammation as the sole cause of EH. Management relies on histopathology and clinical risk factors. Although PTEN, Ki-67, p53, cytokines, and multi-omic profiles show promise, they remain largely experimental methods. LNG-IUS and other progestins require monitoring, whereas hysterectomy is definitive for eligible patients with EIN/atypical EH. Advancements in precision care hinge on the validation of biomarkers that enhance decision-making and outcomes beyond clinical and histological evaluations.

Author Contributions

Conceptualization, A.A. (Arystanbek Atykanov); methodology, A.A. (Albina Aktanbekova); software, A.A. (Argen Alymkulov); validation, A.Z.; data curation, A.A. (Albina Aktanbekova); writing—original draft preparation, A.A. (Argen Alymkulov), A.Z., and A.A. (Arystanbek Atykanov); writing—review and editing, A.A. (Arystanbek Atykanov). All authors have read and agreed to the published version of the manuscript.

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