

METABOLIC LIVER DYSFUNCTION AND ALTERED STEROID METABOLISM IN ENDOMETRIAL HYPERPLASIA

(Literature Review)

¹Sharipova N. M.

²Musakhodjaeva D. A.

¹Eshimbetova G. Z.

²Azizova Z. Sh.

¹Shoikramova N. Kh.

¹Center for the Development of Professional Qualifications of Medical Workers,
Ministry of Health of the Republic of Uzbekistan

²Institute of Immunology and Human Genomics, Academy of Sciences of the
Republic of Uzbekistan

Abstract

Endometrial hyperplasia develops in the setting of prolonged disturbance of hormonal regulation, yet the conventional concept of unopposed estrogen exposure does not fully explain the clinical and metabolic heterogeneity of the disease. Obesity, insulin resistance, hyperinsulinemia, dyslipidemia and ovulatory dysfunction are frequent in affected women and are also closely linked to metabolic liver dysfunction. This narrative review examines clinical evidence connecting liver metabolic status, steroid metabolism and endometrial hyperplasia. A structured PubMed/MEDLINE search covered 2010–2026, with earlier seminal studies retained when they were essential for understanding hepatic SHBG regulation or local steroid metabolism. Thirty-one topic-specific publications were included in the qualitative synthesis, and the review was organized in accordance with SANRA principles. The most consistent clinical associations were observed for obesity and insulin resistance, whereas evidence for an independent role of dyslipidemia was less uniform. Direct studies of steatotic liver disease in histologically confirmed endometrial hyperplasia remain scarce. Metabolic studies, however, consistently associate hepatic fat accumulation and insulin resistance with lower sex hormone-binding globulin

(SHBG), a change that may alter steroid bioavailability without a marked increase in total circulating hormone concentrations. Current evidence therefore supports metabolic liver dysfunction as a potential component of a broader metabolic-hormonal phenotype rather than an established independent cause of endometrial hyperplasia. Studies that assess anthropometric variables, HOMA-IR, lipid profile, liver-related markers, SHBG and steroid hormones within the same cohort, while accounting for age, ovulatory function and menopausal status, are required to define the contribution of the liver more precisely.

Keywords: Endometrial hyperplasia; metabolic liver dysfunction; MASLD; insulin resistance; SHBG; estradiol; steroid metabolism; obesity.

Introduction

Endometrial hyperplasia (EH) comprises morphologically heterogeneous proliferative changes of the endometrium that differ in biological behavior and risk of neoplastic transformation. The current two-tier classification distinguishes hyperplasia without atypia from atypical hyperplasia, the latter corresponding in clinical practice to endometrial intraepithelial neoplasia (EIN) [2–5]. This distinction has direct therapeutic implications: hyperplasia without atypia is generally managed as a hormone-dependent benign process, whereas EIN/atypical hyperplasia requires exclusion of concurrent endometrial carcinoma and closer surveillance [3].

The conventional pathogenetic model of EH is based on prolonged estrogenic stimulation in the absence of adequate progesterone opposition. This model explains the association of EH with chronic anovulation, polycystic ovary syndrome (PCOS), obesity, and exogenous estrogen exposure. In clinical populations, however, EH rarely occurs in the setting of an isolated hormonal disturbance. Abdominal obesity, insulin resistance, hyperinsulinemia, impaired glucose tolerance, and atherogenic dyslipidemia frequently coexist [6–14].

These abnormalities are relevant not merely as comorbid conditions. They influence the production and clearance of sex steroids, synthesis of sex hormone-binding globulin (SHBG), ovulatory function, and intracrine steroid metabolism. The liver participates in several of these processes: it regulates carbohydrate and lipid metabolism, synthesizes SHBG, and contributes to steroid

biotransformation. Despite this central metabolic role, the hepatic component has rarely been evaluated in EH as a distinct element of the clinical-metabolic phenotype.

The current concept of metabolic dysfunction-associated steatotic liver disease (MASLD) has renewed interest in the relationship between hepatic steatosis and reproductive or hormone-dependent disorders. MASLD is defined by hepatic steatosis together with at least one cardiometabolic risk factor, provided that no alternative condition changes the classification of steatotic liver disease [21]. An important consequence of this definition is that elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) is not equivalent to MASLD, while normal aminotransferase activity does not exclude steatosis. This distinction is particularly important in gynecologic research: “metabolic liver dysfunction” should be operationally defined separately from a diagnosis of MASLD.

This review aims to analyze clinical and translational evidence on the relationships among metabolic liver dysfunction, altered steroid metabolism, and endometrial hyperplasia, to assess the strength of evidence for individual links within this relationship, and to identify the parameters most relevant to comprehensive investigation of women with EH.

Materials and Methods

This work was conducted as a structured narrative review. Search planning and presentation of evidence were guided by the SANRA principles, including a clear rationale and objective, transparent description of the literature search, appropriate referencing, and differentiation of levels of evidence [1]. The search was completed on September 17, 2026.

The primary search was performed in PubMed/MEDLINE for publications dated from January 1, 2010, through September 17, 2026. Search combinations included “endometrial hyperplasia”, “endometrial intraepithelial neoplasia”, and “atypical endometrial hyperplasia” together with “obesity”, “insulin resistance”, “hyperinsulinemia”, “HOMA-IR”, “metabolic syndrome”, “dyslipidemia”, “fatty liver”, “NAFLD”, “MASLD”, “sex hormone-binding globulin”, “SHBG”, “estradiol”, “progesterone”, “androgen”, and “steroid metabolism”. Search blocks were combined with the Boolean operators AND and OR. Reference lists

of major clinical guidelines, systematic reviews, and the most relevant original studies were also screened.

Studies of adult women with histologically confirmed EH or EIN/atypical hyperplasia were eligible when they assessed anthropometric measures, carbohydrate or lipid metabolism, insulin resistance, liver-related parameters, SHBG, or steroid profiles. For the analysis of liver–SHBG relationships, studies in other female populations and mixed adult populations were included when they directly characterized hepatic fat, MASLD/NAFLD, SHBG expression, or hepatic lipogenesis. Studies of endometrial carcinoma were used only as supportive evidence and were not substituted for data obtained in EH. Case reports, publications with insufficient description of the variables of interest, studies in which EH could not be distinguished from other pathology, and animal experiments were excluded.

Earlier publications were included selectively when they were fundamental to the analysis of androgen profiles, local estrogen metabolism, or IGF-dependent proliferative signaling in hyperplastic endometrium [29–32]. The final thematic synthesis included 31 topic-specific publications: 22 original clinical or translational studies, five systematic reviews or meta-analyses, and four clinical guidelines. Because of its narrative design, the review was not intended to generate a pooled effect estimate and was not reported as a PRISMA systematic review.

Clinical and Metabolic Profile of Women with Endometrial Hyperplasia

Excess body weight is the most consistently reported clinical marker of metabolic disturbance in EH. In the study by Heller et al., median body mass index (BMI) was 38 kg/m² in women with hyperplasia compared with 30 kg/m² in women with abnormal uterine bleeding and proliferative endometrium [6]. In a cohort of 916 symptomatic premenopausal women, BMI $\geq$ 30 kg/m² was associated with approximately a fourfold higher likelihood of complex hyperplasia or endometrial carcinoma after adjustment for other clinical variables [8]. A systematic review by Wise et al. likewise found a consistent dose-dependent association of BMI with complex hyperplasia and endometrial carcinoma in premenopausal women [7]. The numerical risk estimates from these studies should not be extrapolated to all forms of EH because several analyses combined

hyperplasia with carcinoma, although the direction of the association has been reproducible.

BMI captures overall excess body mass but provides less information about fat distribution. Central adiposity is more informative for the endocrine-metabolic phenotype because it is closely related to insulin resistance and hepatic steatosis. In the study by Kaya et al., obesity and waist circumference >88 cm were more frequent among women with benign endometrial pathology, including polyps and hyperplasia without atypia; insulin resistance was also more common in the same group [12]. The main limitation is that polyps and EH were analyzed together. Even so, the findings support assessment of abdominal adiposity in addition to BMI.

The relationship with carbohydrate metabolism is supported more directly. In the prospective cross-sectional study by Shan et al., 194 of 314 women had EH. Higher insulin concentrations and HOMA-IR were associated with both hyperplasia without atypia and atypical hyperplasia; at HOMA-IR ≥ 2.95 , the odds ratios were 8.48 and 18.72, respectively, compared with controls [9]. The threshold of 2.95 was derived within that particular sample and is not a universal diagnostic cutoff. The study nevertheless demonstrates that hyperinsulinemia is already present at the hyperplastic stage rather than only after development of endometrial carcinoma.

Table 1. Key clinical studies of the metabolic profile in endometrial hyperplasia

Study	Design / sample	Group	Key finding	Limitation
Heller et al., 2011 [6]	Retrospective n=145	EH vs proliferative endometrium	Median BMI 38 vs 30 kg/m ²	Small sample; older classification
Shan et al., 2014 [9]	Prospective cross-sectional n=314	194 EH; DPE; EC; controls	Insulin and HOMA-IR associated with both non-atypical and atypical EH	Cross-sectional; HOMA-IR cutoff is population-specific
Özdemir et al., 2015 [11]	Observational n=199	EH/EC vs normal endometrium	More MetS, diabetes, obesity, hyperglycemia; adverse lipid profile	EH and carcinoma combined
Wise et al., 2016 [8]	Cohort n=916	Complex EH/EC	BMI ≥ 30 kg/m ² associated with ~4-fold higher likelihood of the composite outcome	Composite EH/EC outcome

Study	Design / sample	Group	Key finding	Limitation
Kaya et al., 2019 [12]	Cross-sectional n=168	Polyp/non-atypical EH	More obesity, waist >88 cm and insulin resistance; glucose >110 mg/dL associated with pathology	Polyps and EH combined
Zhong et al., 2023 [14]	Cross-sectional n=234 PCOS	33 EH	Higher BMI and triglycerides; lower HDL-C and SHBG	PCOS-specific population
Wei et al., 2026 [17]	Retrospective n=616	Simple/complex EH	Obesity, diabetes/insulin resistance, and PCOS more frequent in complex EH	Older classification differs from current WHO system

A similar pattern has been reported in perimenopausal women. Kacalska-Janssen et al. identified markers of insulin resistance in 57.1% of women with histologically abnormal endometrium compared with 31.8% of women with normal endometrium; the prevalence of insulin resistance was 52.6% in the non-atypical hyperplasia subgroup [10]. Clinically, impaired insulin sensitivity may be present despite normal fasting glucose. In the study by Mitsuhashi et al., a 75-g oral glucose tolerance test in women with atypical hyperplasia or endometrial carcinoma identified insulin resistance in approximately half of the participants and abnormal glucose metabolism in more than half [13]. These data are not specific to non-atypical EH, but they illustrate the limitations of fasting glucose alone.

Metabolic syndrome combines abdominal obesity, disordered glucose metabolism, dyslipidemia, and hypertension. Özdemir et al. reported a higher prevalence of metabolic syndrome, diabetes mellitus, overall and abdominal obesity, hyperglycemia, and an adverse lipid profile among women with endometrial hyperplasia or carcinoma, particularly after menopause [11]. Chernyshova et al. similarly found that hyperplastic/neoplastic endometrial pathology accompanied by metabolic syndrome was more often associated with higher estrogen, testosterone, and insulin concentrations and lower progesterone levels [16]. The inclusion of different endometrial conditions in the same analyses limits causal interpretation but underscores the close coexistence of metabolic and hormonal abnormalities.

PCOS provides a clinical model in which chronic anovulation, hyperandrogenism, and insulin resistance converge to produce a particularly unfavorable environment for endometrial proliferation. Among 234 women with PCOS who underwent hysteroscopy and biopsy, those with EH had higher BMI and triglyceride levels, lower HDL-C and SHBG, and longer menstrual cycles [14]. A 2026 meta-analysis of nine retrospective studies involving 6,064 women with abnormal uterine bleeding found an association between PCOS and EH (pooled OR 3.09, 95% CI 2.49–3.82) [15]. This association cannot be attributed to a single mechanism because PCOS simultaneously affects ovulation, androgen status, insulin sensitivity, and SHBG.

The lipid profile has been studied less extensively in EH. Several reports describe higher total cholesterol, LDL-C, and triglycerides and lower HDL-C [11,14]. Dyslipidemia, however, is strongly correlated with BMI, abdominal obesity, and insulin resistance, and an independent effect of individual lipid fractions on the development of EH has not been established. In a 2026 clinical study of 616 premenopausal women, obesity, diabetes/insulin resistance, and PCOS were more frequent in women with more complex hyperplasia, supporting the concept of a gradient of metabolic disturbance. The authors used the older simple/complex hyperplasia classification, which does not correspond directly to the current two-tier system [17].

Metabolic Liver Dysfunction and the Position of MASLD

Obesity, insulin resistance, hypertriglyceridemia, and dysglycemia are the same cardiometabolic features that underpin MASLD. The condition of the liver therefore becomes relevant in women with EH who have a pronounced metabolic phenotype. There are two reasons for this. Hepatic steatosis may serve as a marker of the severity of systemic metabolic dysfunction, and the liver may also influence hormonal bioavailability directly through SHBG synthesis and steroid metabolism.

Current nomenclature requires precise use of terms. According to the 2024 EASL–EASD–EASO guidelines, MASLD is diagnosed when hepatic steatosis is present together with at least one cardiometabolic risk factor, in the absence of harmful alcohol use or another condition that places the patient in a different category of steatotic liver disease [21]. A stepwise approach to fibrosis risk

stratification is recommended, beginning with FIB-4 and followed, when indicated, by imaging-based assessment, particularly transient elastography. ALT, AST, and GGT may be abnormal in MASLD, but elevations are not diagnostic criteria, and normal values do not exclude steatosis.

Few studies have objectively confirmed MASLD and compared it with histologically verified EH. More evidence is available for endometrial thickness and endometrial carcinoma. In a population-based study of 8,594 postmenopausal women, the prevalence of MAFLD increased with endometrial thickness, and an association with thickness ≥ 5 mm persisted after adjustment for age [22]. This result cannot be interpreted as evidence of a relationship with EH: ultrasonographic endometrial thickness is not equivalent to a histologic diagnosis, and the MAFLD criteria used in that study differ from current MASLD criteria. The study nevertheless suggests that hepatic and endometrial metabolic phenotypes may coexist.

Supportive epidemiologic evidence has also been reported for endometrial carcinoma. In a nationwide Korean cohort of more than 2.3 million women aged 20–39 years, a higher fatty liver index was associated with a higher risk of early-onset endometrial cancer; the association persisted after adjustment for obesity and showed a dose-response pattern [23]. For the present review, these findings provide only indirect support for biological plausibility. Endometrial cancer should not be used as a surrogate for EH, and the fatty liver index does not replace imaging or histologic confirmation of steatosis.

A major interpretive problem is the overlap of risk factors. A woman with visceral obesity and insulin resistance simultaneously has a higher probability of EH, hepatic steatosis, low SHBG, and ovulatory dysfunction. Even a statistically robust correlation between hepatic steatosis and EH would not, in this setting, demonstrate an independent hepatic effect. Models designed to assess an independent contribution must account for BMI or waist circumference, HOMA-IR, diabetes, PCOS, age, and menopausal status.

ALT, AST, GGT, alkaline phosphatase (ALP), bilirubin, and albumin remain useful in a research protocol, but they characterize different aspects of liver status. Aminotransferases and GGT may reflect hepatocellular injury and metabolic context, whereas albumin and bilirubin are more closely related to synthetic and excretory function and may remain normal in uncomplicated steatosis.

“Metabolic liver dysfunction” should therefore be defined by a prespecified combination of clinical, biochemical, and, when available, imaging criteria rather than by a single laboratory value.

SHBG and Steroid Metabolism as a Potential Link

SHBG is synthesized predominantly by hepatocytes and binds circulating androgens and estradiol, thereby influencing the balance between bound and bioavailable hormone fractions. Its concentration therefore lies at the intersection of hepatic metabolism and steroid regulation. Low SHBG is common in obesity, insulin resistance, type 2 diabetes, and steatotic liver disease [24–28].

The SWAN findings are particularly informative for women: among 208 midlife women, greater hepatic fat and lower SHBG were independently associated with higher insulin concentrations after adjustment for overall adiposity, and the combination of low SHBG with greater liver fat corresponded to the least favorable metabolic profile [24]. In the Rotterdam population study and a subsequent meta-analysis of 16 studies, low SHBG was associated with NAFLD in both sexes, including women [25].

Reduced SHBG cannot be explained solely by a direct effect of insulin. Hepatic SHBG gene expression depends on hepatocyte nuclear factor 4 alpha (HNF4 α) and hepatocellular lipid metabolism. The experimental and clinical model proposed by Pugeat et al. links excess monosaccharide exposure to increased lipogenesis, reduced HNF4 α activity, and lower SHBG expression [26]. Human liver tissue studies have demonstrated inverse relationships of HOMA-IR and hepatic triglyceride content with HNF4 α and SHBG expression [27]. In humans, the rate of de novo lipogenesis has also been inversely related to circulating SHBG, particularly in women [28]. These findings support SHBG as more than a carrier protein; it may also reflect the metabolic state of the liver.

For the endometrium, the relevant point is that altered SHBG can modify steroid bioavailability without a marked rise in total circulating hormone concentrations. This may help explain heterogeneity across EH studies: the absence of systemic hyperestradiolemia does not exclude increased steroid exposure at the tissue level. In an earlier study by Vitoratos et al., premenopausal women with adenomatous endometrial hyperplasia had higher estradiol, testosterone, androstenedione, and DHEA-S, while SHBG did not differ significantly [29].

Another study found no convincing systemic hyperestrogenemia in EH but described alterations in local estrogen metabolism and steroid-metabolizing enzyme activity within abnormal endometrium [30].

Table 2. Strength of evidence for the main components of the metabolic-hormonal model

Relationship	Evidence	Interpretation	Level
Obesity → EH	Clinical studies and systematic review [6–8]	Consistent association; some studies combine EH with cancer	High
Insulin resistance → EH	Direct EH studies [9,10,12,13]	Present before overt diabetes; causality not fully established	Moderate-high
Dyslipidemia → EH	Observational data [11,14]	Difficult to separate from obesity and insulin resistance	Moderate-low
Hepatic steatosis → EH	Limited direct data; endometrial thickness and cancer provide indirect evidence [22,23]	Requires histologically confirmed EH and objective steatosis assessment	Low
Hepatic fat/insulin resistance → lower SHBG	Population, tissue, and metabolic studies [24–28]	Reproducible association; mechanisms involve HNF4α and lipogenesis	High (non-EH)
Low SHBG → altered steroid bioavailability → EH	Clinical and mechanistic evidence [14,24–31]	Biologically plausible; mediating role in EH remains unproven	Moderate

Evidence from PCOS further supports the importance of local steroid regulation. Bacallao et al. reported altered activities of steroid sulfatase, estrogen sulfotransferase, and 17β-hydroxysteroid dehydrogenases in the endometrium of women with PCOS and hyperplasia [31]. Peripheral hormone concentrations and the actual steroid milieu within the endometrium are therefore not necessarily equivalent.

Progesterone opposition is as important as estrogenic stimulation. In women of reproductive age, inadequate progesterone exposure more often reflects chronic anovulation than isolated “hypoprogesteronemia”. Interpretation of progesterone without information on cycle phase and ovulation is therefore of limited value. PCOS illustrates the convergence of chronic anovulation, hyperandrogenism,

insulin resistance, and low SHBG; a 2026 meta-analysis confirms a higher likelihood of EH among women with PCOS and abnormal uterine bleeding [15]. The androgen profile should not be treated as the opposite of an estrogenic profile. When SHBG falls, the free fraction of testosterone increases, and some androgens serve as substrates for peripheral aromatization in adipose tissue. Hyperandrogenism, obesity, and relative estrogen excess may therefore coexist. This pattern is especially characteristic of PCOS, although components of the same combination have also been described in EH outside PCOS [14,16,29].

Insulin Resistance within the Metabolic-Hormonal System

Insulin resistance provides the most convincing link between the clinical metabolic phenotype of EH, liver status, and steroid metabolism. In its early stages it is accompanied by compensatory hyperinsulinemia, so normal fasting glucose does not exclude substantial impairment of insulin sensitivity. For research purposes, measurement of insulin and calculation of HOMA-IR allow this phenotype to be characterized quantitatively, although no universal HOMA-IR cutoff applies across all populations.

Hepatic insulin resistance disrupts regulation of gluconeogenesis and lipid metabolism and is closely associated with intrahepatic triglyceride accumulation. De novo lipogenesis increases in this setting, while SHBG concentrations decline [24,26–28]. In a woman with EH, the same concentration of total estradiol or testosterone may therefore correspond to different proportions of bioavailable hormone depending on SHBG.

Insulin may also be relevant independently of steroid transport. Hyperplastic endometrium has been shown to express more insulin-like growth factor I receptor and to exhibit greater AKT pathway activation than normal proliferative endometrium [32]. These observations do not establish systemic hyperinsulinemia as an initiator of EH, but they provide a molecular basis for interaction between metabolic signaling and hormone-dependent proliferation.

Clinical studies of metabolic interventions have not yet established causality. A systematic review of weight loss found histologic regression of EH in some women after bariatric surgery, but the number of observations was small and the quality of evidence was insufficient to isolate an independent effect of weight reduction [18]. An updated Cochrane review of metformin included seven

randomized trials with 387 participants and rated the certainty of evidence as low or very low for most outcomes [19]. In an observational study of 202 women, the addition of metformin and weight reduction was associated with a higher rate of regression, but these interventions were delivered alongside progestin therapy and their effects depended on baseline metabolic status [20].

These findings support the clinical relevance of metabolic phenotyping but do not justify considering metformin, weight loss, or correction of liver abnormalities as specific treatment for EH outside established indications. For pathogenetic research, a more relevant point is that metabolic abnormalities may influence disease course and response to hormonal therapy; assessing them together with SHBG and the steroid profile is therefore justified as a research strategy.

Integrated Model and Its Limitations

The available evidence supports a working model in which visceral obesity and insulin resistance provide a common metabolic background for endometrial proliferation and hepatic steatosis. Hepatic fat accumulation and altered hepatic lipogenesis are associated with reduced SHBG. At the same time, chronic anovulation reduces progesterone opposition, while adipose tissue maintains peripheral aromatization of androgens. The endometrium is consequently exposed to several convergent stimuli: prolonged estrogenic action, altered steroid bioavailability, and insulin/IGF-dependent growth signaling.

The strongest evidence supports the early links in this sequence: the association of EH with obesity and insulin resistance [6–15], and the association of hepatic fat with low SHBG [24–28]. Evidence is considerably weaker for the transition from liver dysfunction to a specific steroid profile in women with EH. Fewer studies still assess objective liver status, SHBG, sex steroids, and histologic subtype of hyperplasia within the same cohort.

An alternative explanation remains plausible: hepatic steatosis may not be an independent component of the pathway but rather a marker of the same metabolic disturbance that increases the probability of EH through obesity, insulin resistance, and anovulation. Distinguishing these possibilities requires multivariable analysis. Persistence of associations between liver-related variables, SHBG, and the steroid profile after adjustment for BMI, waist circumference, HOMA-IR, PCOS, age, and menopausal status would support an

additional hepatic contribution. Loss of these associations after adjustment would suggest that hepatic abnormalities primarily reflect the severity of the broader metabolic phenotype.

Morphologic classification is another source of heterogeneity. Many older studies used the categories of simple, complex, and atypical hyperplasia. Current practice is based on the two-tier distinction between hyperplasia without atypia and EIN/atypical hyperplasia [2–5]. Comparisons across publication periods therefore require caution because study groups are not always equivalent in either risk or morphologic criteria.

Age and reproductive status may also modify the observed associations. In women of reproductive age, chronic anovulation and PCOS may predominate; in perimenopause, increasing instability of ovulatory cycles becomes relevant; after menopause, peripheral aromatization and the metabolic state of adipose tissue assume greater importance. Comparisons of hormone concentrations without stratification for these factors may obscure clinically meaningful patterns.

Clinical and Research Implications of Comprehensive Assessment

The diagnosis of EH remains histologic. HOMA-IR, lipid measurements, liver-related markers, and SHBG cannot replace endometrial biopsy or reliably distinguish hyperplasia without atypia from EIN/atypical hyperplasia. Current guidelines focus on histologic verification, exclusion of concurrent carcinoma, progestin or surgical treatment, and surveillance [3–5]. Metabolic variables serve a different purpose: they characterize the biological background in which the proliferative process develops and persists.

For clinical research, it is useful to organize variables by physiological domain. BMI and waist circumference describe the extent and distribution of adipose tissue; glucose, insulin, and HOMA-IR characterize carbohydrate metabolism and insulin sensitivity; triglycerides, HDL-C, LDL-C, and total cholesterol define the lipid profile; ALT, AST, GGT, ALP, bilirubin, and albumin describe different aspects of liver status. SHBG links the metabolic and hormonal domains, whereas estradiol, progesterone, and androgens characterize the steroid environment. Interpreting each marker in isolation is less informative than examining their relationships within the same patient.

Particular care is required in defining a group labeled “metabolic liver dysfunction”. If classification is based only on aminotransferases, that group is not equivalent to MASLD and should not be named as such. If imaging confirms steatosis and cardiometabolic criteria are present, current MASLD nomenclature can be applied [21]. Prespecifying an operational definition before statistical analysis improves reproducibility and reduces the risk of combining biologically different liver phenotypes.

A multivariable approach is the most informative way to test the hypothesis that liver status is related to steroid metabolism. In addition to simple group comparisons, correlations of SHBG and steroid hormones with HOMA-IR, triglycerides, GGT, and other liver-related variables should be assessed, followed by models adjusted for age, BMI or waist circumference, PCOS or evidence of ovulatory dysfunction, and menopausal status. Such analyses can determine whether the hepatic component has an association with the hormonal profile that is independent of the major metabolic confounders.

If a study population includes both hyperplasia without atypia and atypical hyperplasia/EIN, histologic subtype should be analyzed separately. Current evidence allows the possibility of greater metabolic disturbance in more complex forms of hyperplasia [9,17], but it remains insufficient to establish a rigid risk gradient. EH should also not be combined with endometrial carcinoma in the primary analysis, because this practice, common in earlier studies, makes interpretation of the hyperplastic process itself more difficult.

Gaps in the Evidence

The principal gap in the literature is not a lack of information about obesity or insulin resistance, but the absence of studies in which all major components are assessed concurrently. EH studies usually focus on BMI and carbohydrate metabolism; liver studies examine MASLD and SHBG outside a gynecologic setting; hormonal studies often measure only selected steroids. This fragmentation makes it difficult to determine whether the liver is an independent participant in the pathogenetic pathway or primarily a marker of systemic metabolic dysfunction.

It remains unknown whether associations between liver-related variables and SHBG persist in women with histologically confirmed EH after accounting for

BMI and HOMA-IR. Evidence is also insufficient to determine whether this profile differs between hyperplasia without atypia and EIN/atypical hyperplasia. The combination of biochemical liver markers, objectively documented steatosis, SHBG, and free or calculated sex-steroid fractions has rarely been examined within a single cohort.

Future studies should distinguish direct evidence from supportive evidence. Endometrial carcinoma studies are useful for assessing biological plausibility but should not substitute for EH-specific data. Likewise, the association between low SHBG and MASLD is well supported, but it does not by itself demonstrate that the liver alters the risk of hyperplasia through SHBG. These transitions in the proposed pathway require purpose-designed clinical studies.

Conclusion

Endometrial hyperplasia is closely associated with metabolic abnormalities, particularly obesity and insulin resistance. Dyslipidemia, hyperinsulinemia, and chronic anovulation frequently occur within the same clinical phenotype, but the strength of evidence differs across components. A simple “high estradiol–hyperplasia” model does not capture this heterogeneity: the biological effect of steroid hormones depends on ovulatory status, progesterone opposition, SHBG, and local endometrial metabolism.

The liver is a biologically plausible candidate for linking metabolic and hormonal disturbances. Hepatic fat accumulation, insulin resistance, and de novo lipogenesis are consistently associated with lower SHBG, while SHBG influences the bioavailability of sex steroids to target tissues. In EH, this sequence has been only partly demonstrated. Direct studies assessing endometrial histology, liver status, HOMA-IR, SHBG, and the steroid profile within the same cohort remain scarce.

Metabolic liver dysfunction is therefore best regarded as a potential component of the broader metabolic-hormonal phenotype of EH rather than an established independent cause of the disease. Integrated assessment of anthropometric, carbohydrate, lipid, hepatic, and hormonal variables with multivariable statistical analysis may clarify the place of the liver within this system and determine whether its association with steroid metabolism persists independently of obesity and insulin resistance.

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