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THE ROLE OF INSULIN RESISTANCE IN THE DEVELOPMENT OF ENDOMETRIAL HYPERPLASIA IN PREMENOPAUSAL WOMEN

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Abstract
Endometrial hyperplasia in women of premenopausal age represents an important problem in gynecology because of its relatively high occurrence and the possibility of progression to malignant disease. Metabolic syndrome and excessive body weight are considered major contributing factors that increase the likelihood of abnormal proliferative processes in the endometrium. These conditions are frequently associated with menstrual irregularities, infertility, and an early onset of menarche. In a clinical observation involving 42 patients, mild obesity was identified in 40% of cases, moderate obesity in 35%, and severe obesity in 15% of the examined women. The obtained data suggest a significant association between metabolic disorders and the development of endometrial hyperplasia in the premenopausal period, underlining the importance of careful medical supervision and timely evaluation of women who present with metabolic risk factors.

Keywords: Endometrial hyperplasia, abnormal uterine bleeding, metabolic syndrome, obesity, premenopausal period.

Introduction

Endometrial hyperplasia remains one of the most important challenges in modern gynecology, particularly among women in the premenopausal stage, when hormonal instability increases the impact of metabolic disturbances on the reproductive system. According to international clinical and epidemiological studies, the development of proliferative changes in the endometrium is strongly associated with the components of metabolic syndrome, including obesity, insulin resistance, hyperinsulinemia, and lipid metabolism disorders. These metabolic abnormalities contribute to the

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development of chronic hyperestrogenism, which creates favorable conditions for the emergence of hyperplastic processes in endometrial tissue.

Reports from the World Health Organization and the International Agency for Research on Cancer indicate that endometrial cancer consistently ranks among the most common malignancies of the female reproductive system. According to estimates from the GLOBOCAN project, more than 417,000 new cases of endometrial cancer and approximately 97,000 related deaths were recorded worldwide in 2020 [7,11,16]. These figures highlight the significant medical and social burden of this disease.

Importantly, a considerable proportion of malignant endometrial tumors develop on the background of long-standing benign or precancerous endometrial alterations. Of particular clinical relevance is the observation that metabolic syndrome not only increases the likelihood of developing endometrial hyperplasia but is also associated with a higher risk of recurrence and malignant transformation of these lesions.

Objective:

To investigate the impact of metabolic syndrome on the risk of developing endometrial hyperplasia in women during the premenopausal period.

Materials and Methods

In accordance with the objectives of the study, a prospective investigation was conducted involving 42 women of premenopausal age who were diagnosed with neoplastic changes of the endometrium. All participants were monitored at the Republican Specialized Scientific and Practical Medical Center of Mother and Child Health. The research included a comprehensive assessment of clinical and laboratory parameters in patients presenting with abnormal uterine bleeding (AUB) [1,2]. Particular attention was paid to evaluating the role of metabolic syndrome as a potential risk factor for the development of endometrial hyperplasia, as well as to assessing the effectiveness of diagnostic approaches used for detecting endometrial pathology during the premenopausal period.

Results and Discussion

During the study, the frequency of clinical manifestations of endometrial hyperplasia was evaluated in 42 premenopausal women, the majority of whom demonstrated signs of metabolic syndrome. Menstrual cycle disturbances were the most common complaints reported by the patients. Oligomenorrhea was observed in 14 women (33%), intermenstrual spotting occurred in 16 patients (38%), while increased menstrual volume and duration consistent with hyperpolymenorrhea were recorded in 19 cases (45%). Pelvic pain and a sensation of heaviness in the lower abdomen were noted in 13 women (31%).

The mean age of the examined patients was 47.6 ± 2.5 years, which corresponds to a period characterized by pronounced hormonal and metabolic changes. The presence of clinical symptoms in combination with obesity and other components of metabolic syndrome highlights their important role in the development of hyperplastic processes in the endometrium among premenopausal women [4,8].

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In many of the examined patients, menarche occurred at an early age. Specifically, 20 women (47.6%) reported the onset of menstruation between 9 and 12 years of age, while 14 patients (33.3%) experienced menarche at 13–14 years. Later menarche (15 years or older) was observed in 8 women (19.1%). A regular menstrual cycle was established immediately after menarche in 32 participants (76.2%), whereas in 10 women (23.8%) menstrual regularity developed during the first year after its onset.

Assessment of menstrual function over the previous 2–3 years demonstrated a high prevalence of pathological symptoms. Heavy menstrual bleeding was reported by 32 patients (76.2%), prolonged menstruation lasting more than seven days occurred in 20 women (47.6%), and dysmenorrhea was observed in 15 patients (35.7%) [5,9,12]. Additionally, delayed menstruation lasting from two to four months was documented in 28 women (66.7%), which may be associated with hormonal and metabolic disturbances typical of the premenopausal period.

The duration of abnormal uterine bleeding ranged from 1 to 9 years, with an average duration of 5.6 ± 1.7 years. This finding indicates a prolonged course of the condition and a tendency for delayed medical consultation. In most patients, the onset of sexual activity occurred between the ages of 20 and 23 years (52.5%), while 35% reported sexual debut at 17–19 years and 12.5% after the age of 24 (Table 1).

Table 1 Characteristics of menstrual function in the examined women (n = 42)

Indicator	Absolute number	%
Age at menarche		
9–12 years	20	47.6
13–14 years	14	33.3
≥15 years	8	19.1
Establishment of regular menstrual cycle		
Immediately after menarche	32	76.2
Within the first year	10	23.8
Menstrual cycle disorders (during the last 2–3 years)		
Heavy menstrual bleeding	32	76.2
Duration >7 days	20	47.6
Painful menstruation	15	35.7
Menstrual delays (2–4 months)	28	66.7
Duration of abnormal uterine bleeding (years)	1–9	5.6 ± 1.7

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The mean body mass index (BMI) among the examined patients was 32.8 ± 6.9 kg/m², indicating a high prevalence of obesity and significant metabolic disturbances in the study population. The analysis of BMI distribution demonstrated that mild obesity was identified in 17 women (40.5%), moderate obesity in 15 patients (35.7%), and severe obesity in 6 women (14.3%). In contrast, a normal BMI was recorded in only 4 participants (9.5%).

These findings emphasize the important role of obesity as a major component of metabolic syndrome in the development of endometrial hyperplasia among women during the premenopausal period (Table 2).

Table 2 Degrees of obesity in patients with endometrial hyperplasia

BMI Category	Number of Patients	Proportion (%)
Obesity Grade I (mild)	17	40.5
Obesity Grade II (moderate)	15	35.7
Obesity Grade III (severe)	6	14.3
Normal BMI	4	9.5
Mean BMI (kg/m²)	42	32.8 ± 6.9

Among the examined women, somatic comorbidities were predominantly associated with metabolic disturbances, particularly affecting the urinary and digestive systems. Urolithiasis was diagnosed in 24 patients (57.1%), while chronic cystitis was observed in 17 women (40.5%). Regarding digestive system disorders, the most frequently detected conditions were hepatic steatosis (non-alcoholic fatty liver disease) in 14 patients (33.3%) and chronic cholecystitis in 9 women (21.4%). Additionally, chronic gastritis was reported in 8 patients (19.0%) and chronic hepatitis in 5 women (11.9%) [6,10].

A significant proportion of the participants also exhibited anemic syndrome, likely related to the prolonged course of abnormal uterine bleeding. Mild iron-deficiency anemia was diagnosed in 13 women (31.0%), moderate anemia in 17 patients (40.5%), and severe anemia in 6 women (14.3%) (Table 3).

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Table 3 Somatic comorbidities in women with endometrial hyperplasia during the premenopausal period

Condition	Number of Patients	Proportion (%)
Urinary system disorders		
Urolithiasis	24	57.1
Chronic cystitis	17	40.5
Digestive system disorders		
Non-alcoholic fatty liver disease (hepatic steatosis)	14	33.3
Chronic cholecystitis	9	21.4
Chronic gastritis	8	19.0
Chronic hepatitis	5	11.9
Anemic syndrome		
Mild	13	31.0
Moderate	17	40.5
Severe	6	14.3

A majority of women with endometrial hyperplasia during the premenopausal period exhibited hormonal imbalances. Elevated estrogen levels were observed in 30 patients (71%), while reduced progesterone levels were noted in 28 women (67%) [4,13,15]. Increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were recorded in 22 (52%) and 25 (60%) patients, respectively, reflecting the typical ovarian functional changes associated with the premenopausal period.

Signs of insulin resistance accompanied by elevated insulin levels were detected in 26 women (62%) [1,9]. Additionally, increased testosterone levels were observed in 12 patients (29%), often in association with polycystic ovary syndrome (PCOS) (Table 4).

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Table 4 Hormonal profile in patients with endometrial hyperplasia

Hormone	Number of Patients with Abnormal Levels	Proportion (%)
Elevated estrogen (estradiol)	30	71
Reduced progesterone	28	67
Elevated luteinizing hormone (LH)	22	52
Elevated follicle-stimulating hormone (FSH)	25	60
Elevated testosterone	12	29
Elevated insulin	26	62

During the course of diagnosis and treatment, curettage of the uterine cavity was performed in 14 women (33.3%), diagnostic hysteroscopy in 17 patients (40.5%), and hysterectomy in 11 women (26.2%). The high frequency of these interventions reflects the complexity of the clinical presentation and the need for surgical management in cases of endometrial hyperplasia associated with metabolic disturbances.

Analysis of reproductive history revealed that 15 patients (35.7%) had cesarean deliveries following full-term pregnancies, while preterm births occurred in 3 women (7.1%). Additionally, 4 patients (9.5%) experienced either non-developing pregnancy or ectopic pregnancy [11,12]. Medical abortions (1–2 cases) were reported in 14 women (33.3%), whereas three or more abortions were recorded in 6 patients (14.3%). Regarding parity, 4 women (9.5%) had six or more deliveries, 11 women (26.2%) had 4–5 deliveries, 13 patients (31%) had fewer than four deliveries, and 14 women (33.3%) were diagnosed with infertility.

Evaluation of concomitant gynecological pathology showed that uterine fibroids of intramural and/or subserous localization were present in 13 patients (31%), indicating a frequent coexistence of fibroids with hyperplastic endometrial processes. Adenomyosis was diagnosed in 6 women (14%), while a combination of fibroids and adenomyosis occurred in 7 patients (17%). Endometrial polyps were detected in 9 women (21%). Furthermore, a history of polycystic ovary syndrome (PCOS) was reported in 18 patients (43%), highlighting the significant role of hormonal and metabolic disturbances in the development of endometrial changes.

Transvaginal ultrasonography revealed echogenic signs of endometrial polyps in 9 patients (21%), endometrial hyperplasia in 34 women (81%), and a combination of endometrial polyps with hyperplasia in 8 patients (19%).

Hysteroscopic examination demonstrated features of endometrial hyperplasia with enhanced vascular patterns and heterogeneous endometrial thickening ranging from 12 to 20 mm in 14 patients (33%). Soft endometrial polyps measuring 3–15 mm was identified in 5 women (12%), and a combination of hyperplasia and polyps was observed in another 5 patients (12%). These findings highlight the importance of comprehensive instrumental evaluation for accurate diagnosis and differentiation of

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endometrial pathologies in the premenopausal period, especially in women with metabolic disturbances (Table 5).

Histological analysis of endometrial biopsies revealed that the most common form of hyperplasia was complex hyperplasia without atypia, diagnosed in 20 women (47.6%). Simple hyperplasia was identified in 15 patients (35.7%), while atypical hyperplasia was found in 5 women (11.9%). In 4 cases (9.5%), endometrial polyps were combined with simple hyperplasia.

Table 5 Concomitant gynecological pathology and findings from instrumental examinations in women with endometrial hyperplasia

Parameter	Number of Patients	Proportion (%)
Concomitant gynecological pathology		
Uterine fibroids (intramural and/or subserous)	13	31.0
Adenomyosis	6	14.3
Combination of fibroids and adenomyosis	7	16.7
Endometrial polyps	9	21.4
History of polycystic ovary syndrome (PCOS)	18	42.9
Transvaginal ultrasound findings		
Echogenic signs of endometrial polyp	9	21.4
Endometrial hyperplasia	34	81.0
Combination of polyp and hyperplasia	8	19.0
Hysteroscopy findings		
Endometrial hyperplasia with vascular changes (12–20 mm)	14	33.3
Endometrial polyps (3–15 mm)	5	11.9
Combination of hyperplasia and polyps	5	11.9

The diversity of morphological forms of endometrial hyperplasia, along with the frequent presence of concomitant polyps, poses significant diagnostic challenges [12,16]. Considering the impact of metabolic syndrome on the progression of these conditions and the increased risk of malignant

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transformation, histological confirmation is an essential step for timely detection and for guiding the appropriate management strategy.

Conclusion

The present study demonstrated that the development of endometrial hyperplastic changes in premenopausal women is influenced by a combination of factors, including metabolic disturbances, excessive body weight, early menarche, menstrual irregularities, infertility, polycystic ovary syndrome (PCOS), as well as concomitant somatic and gynecological disorders. These factors significantly increase the predisposition to both benign and precancerous alterations of the endometrial tissue, as supported by numerous clinical and epidemiological studies.

In particular, a higher incidence of hyperplasia was observed in patients with early onset of menstruation and pronounced ovulatory cycle disturbances, highlighting the central role of hormonal imbalance, which is further exacerbated by obesity and endocrine disorders such as insulin resistance and hyperinsulinemia, characteristic of metabolic syndrome. The morphological diversity of hyperplastic processes, including simple, complex, and atypical forms, necessitates a comprehensive diagnostic approach [8,14].

The most informative methods for early detection and accurate diagnosis of endometrial pathology remain transvaginal ultrasonography, hysteroscopy, and subsequent histological examination of biopsy samples. This integrated approach allows not only for precise characterization of endometrial changes but also for timely assessment of malignant potential, which is critical for developing an appropriate patient management strategy.

Given the increasing prevalence of metabolic syndrome and associated endocrine disorders among premenopausal women, special attention should be directed toward the early identification of endometrial hyperplasia in high-risk groups. Timely diagnosis and monitoring of these patients can improve prognosis, reduce the frequency of complications, and prevent the progression of pathological processes to malignant forms.

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