Original Paper

Integrated Clinicopathological Assessment of Endometrial Polyps as Heterogeneous Proliferative Lesions in Reproductive-Aged Women

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ABSTRACT: Background: Endometrial polyps (EPs) are heterogeneous focal proliferative lesions with variable clinical, ultrasonographic (US), and histopathological features across reproductive age. Objective: To characterize EPs in reproductive-aged women using an integrated clinical, US, histopathological, and immunohistochemical (IHC) approach, with emphasis on age-associated differences. Methods: This retrospective multicenter study included 62 premenopausal women aged 28-49 years with histopathologically confirmed EPs. Participants were equally stratified into Group A (28-38 years, n=31) and Group B (39-49 years, n=31). Clinical, metabolic, US, histopathological, and representative IHC data were comparatively assessed. Results: Abnormal uterine bleeding was significantly more frequent in Group B than in Group A (90.32% vs 41.94%, p<0.001). Group B also showed higher frequencies of irregular cycles, infertility, mixed histological subtypes, and heterogeneous lesion and background endometrial morphology, together with larger lesions and increased endometrial thickness. Glandular crowding was significantly more frequent in Group B (54.84% vs 29.03%, p=0.039), while cystic glandular dilatation, increased gland-to-stroma ratio, nuclear atypia, and disordered proliferative or hyperplastic background endometrium were also more common. Most lesions were solitary and regularly contoured, with a feeding vessel identified in 64.52% of cases. IHC assessment demonstrated loss of PAX2 expression and a high, heterogeneous Ki-67 proliferative index in representative lesions. Conclusion: EPs in reproductive-aged women display age-associated clinical and morphological heterogeneity. Integrating clinical presentation, US morphology, histopathological architecture, and background endometrial features may provide a more comprehensive framework for lesion assessment.

KEYWORDS: *Endometrial polyps, reproductive age, endometrial remodeling, ultrasonography, morphological variability, immunohistochemistry.*

Introduction

Endometrial polyps (EPs) are among the most common focal intrauterine lesions, characterized by localized overgrowths of endometrial glands, stroma, and vascular elements projecting into the uterine cavity.

Histologically, EPs consist of variable proportions of glandular, stromal, fibrous, and vascular components, resulting in considerable morphologic heterogeneity and a broad spectrum of clinical and biological behavior [1].

Although traditionally regarded as benign intracavitary lesions, EPs are increasingly recognized as heterogeneous proliferative endometrial lesions with variable architectural complexity, hormonal responsiveness, proliferative activity, and biological behavior [1-5].

The prevalence of EPs varies according to population characteristics, menopausal status, clinical indication, and diagnostic modality, ranging from approximately 7% to 40% across different cohorts [2-8].

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Their incidence increases progressively with age, particularly during the late reproductive and perimenopausal years, supporting an important role of cumulative hormonal exposure and endometrial remodeling in their development [3,6-8].

In reproductive-aged women, EPs are clinically relevant because they may occur in patients presenting with abnormal uterine bleeding, infertility, recurrent pregnancy loss, or as incidental findings during routine gynecological evaluation.

The pathogenesis of EPs remains incompletely understood and appears multifactorial, involving prolonged estrogenic stimulation, progesterone resistance, altered apoptotic regulation, chronic inflammation, angiogenic activation, and molecular alterations affecting endometrial homeostasis [3,5,7-11].

Current evidence suggests that EP formation reflects complex interactions between hormonal, metabolic, vascular, and inflammatory pathways that promote focal endometrial proliferation and altered tissue remodeling. Several risk factors have been associated with EP development, including advancing reproductive age, obesity, hypertension, diabetes mellitus, tamoxifen exposure, and other hyperestrogenic states [1-5].

Among these, obesity and elevated body mass index (BMI) are particularly relevant because of their association with increased peripheral estrogen production, chronic low-grade inflammation, altered adipokine signaling, and metabolic dysregulation, all of which may contribute to abnormal endometrial proliferation [5,7-11].

These observations suggest that metabolic status may influence not only EP formation, but also lesion morphology and biological profile.

Clinically, EPs present with a heterogeneous spectrum of manifestations. Many lesions remain asymptomatic and are diagnosed incidentally during gynecological imaging, whereas symptomatic EPs are most commonly associated with abnormal uterine bleeding, particularly intermenstrual bleeding, irregular menstrual bleeding, or excessive menstrual blood loss [1-8].

EPs also represent an important consideration in infertility evaluation, as they may interfere with embryo implantation and endometrial receptivity through mechanical, inflammatory, and local molecular mechanisms [3,5,8].

In addition, they may coexist with adenomyosis, leiomyomas, endometriosis, endometrial hyperplasia (EH), and other forms of abnormal endometrial proliferation, further complicating diagnostic interpretation and clinical management.

Transvaginal ultrasonography (TVUS) remains the first-line imaging modality for the evaluation of suspected EPs because of its accessibility, non-invasiveness, and diagnostic utility [1,12-14].

Ultrasonographic (US) assessment includes evaluation of endometrial thickness, lesion morphology, echogenicity, the endometrial-myometrial interface, and associated uterine abnormalities. Doppler examination may further support lesion characterization by identifying vascular features such as a feeding vessel, vascular branching, and lesion perfusion [1,3,5,12-15].

Saline contrast sonohysterography may improve diagnostic accuracy compared with conventional TVUS, particularly in patients with inconclusive findings or suspected focal intracavitary pathology [12-17].

Nevertheless, imaging alone cannot reliably define the full histopathological nature of EPs or exclude hyperplastic, atypical, or architecturally complex changes, making histopathological evaluation essential for definitive diagnosis.

From a morphological perspective, EPs exhibit substantial variability in glandular architecture, stromal composition, vascular patterns, and hormonal responsiveness.

Functional, hyperplastic, atrophic, and mixed patterns have been described [1-5].

Although most EPs are benign, some may demonstrate hyperplastic changes, metaplastic alterations, cytological atypia, or focal proliferative complexity [3,5,7-11].

Immunohistochemical (IHC) evaluation may complement conventional histopathology by providing additional information on proliferative activity, hormonal receptor expression, apoptotic regulation, and early molecular alterations relevant to endometrial homeostasis [3,5,11-19].

An integrated clinical, US, histopathological, and selective immunophenotypic approach may therefore provide a more comprehensive characterization of EPs in reproductive-aged women.

Objective

The aim of this study was to characterize EPs as heterogeneous proliferative lesions in reproductive-aged women using an integrated clinical, US, histopathological, and selective immunophenotypic approach, with particular emphasis on age-related differences, lesion heterogeneity, associated gynecological pathology, and biological variability.

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Methods

This retrospective observational multicenter study included 62 selected cases of histopathologically confirmed EPs diagnosed in premenopausal women evaluated over a five-year period, between January 2021 and January 2026. The study integrated retrospectively collected clinical, US, histopathological, and selective IHC data. The study population consisted of premenopausal women aged 28-49 years with EPs suspected by US examination and subsequently confirmed by histopathological assessment following tissue sampling. For comparative analysis, patients were stratified into two age-defined groups: Group A, including women aged 28-38 years, and Group B, including women aged 39-49 years. This stratification was selected to capture potential clinicopathological differences across the reproductive-age continuum by contrasting an earlier with a later reproductive-age interval, while preserving equal interval width and balanced group size (n=31 in each group). The 39-year threshold was therefore used as an analytical boundary rather than as a predefined biological or clinical cutoff.

Inclusion criteria were premenopausal status, suspected or confirmed EPs identified by US and/or hysteroscopy, histopathological confirmation after biopsy, curettage, or polypectomy, and availability of complete clinical, imaging, and histopathological data.

Exclusion criteria included pregnancy-related conditions, postmenopausal status, incomplete clinical or imaging data, absence of histopathological confirmation, known endometrial carcinoma at inclusion, previous hysterectomy, active pelvic inflammatory disease, and insufficient tissue material for histopathological evaluation.

The analyzed variables included age, BMI, parity, nulliparity, previous abortions, previous cesarean section, smoking status, infertility history, clinical presentation, abnormal uterine bleeding, recurrent pregnancy loss, pelvic pain, dysmenorrhea, dyspareunia, abnormal vaginal discharge, anemia, previous EPs, and recurrent EPs. Metabolic, endocrine, and hormonal variables included obesity, metabolic syndrome, arterial hypertension, diabetes mellitus, insulin resistance, polyendocrine metabolic ovarian syndrome (PMOS), the recently proposed terminology for polycystic ovary syndrome (PCOS) [20], thyroid disorders, previous hormonal therapy, oral contraceptive use, progesterone therapy, intrauterine device use, and fertility treatment. Associated gynecological pathology included adenomyosis, endometriosis, leiomyomas, ovarian cysts or tumors, EH, cervical polyps, and other concomitant uterine or adnexal abnormalities.

US evaluation was performed as part of the diagnostic work-up. TVUS was the primary imaging modality, with transabdominal US used when clinically indicated. Examinations were performed using high-resolution US systems equipped with endocavitary and convex probes.

Saline infusion sonography was performed in selected cases to improve delineation of focal intracavitary lesions, while hysteroscopy was used when clinically indicated for direct lesion visualization, diagnostic assessment, and hysteroscopic polypectomy. US assessment included evaluation of uterine morphology, endometrial thickness, echogenicity, homogeneity, midline appearance, the endometrial-myometrial junction, focal intracavitary lesions, ovarian morphology, and associated pelvic pathology. EPs were characterized according to number, maximal diameter, intracavitary location, contour, echogenicity, echostructure, and extension.

Color and power Doppler were used to assess lesion vascularity, including the presence of a feeding vessel and a detectable vascular pattern.

Tissue sampling was performed after US and/or hysteroscopic identification of EPs, according to clinical indication and procedural availability. Sampling methods included hysteroscopic polypectomy, dilation and curettage, and fractional curettage.

Hysteroscopic polypectomy was preferred whenever feasible because it allowed direct lesion visualization and targeted removal.

Whenever technically possible, EP specimens were submitted separately from the surrounding endometrium. In curettage-based procedures, EP tissue and background endometrium were frequently submitted as combined specimens. All specimens were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, and examined on hematoxylin-eosin-stained sections.

Histopathological evaluation was performed independently by two gynecological pathologists (M.O. and T.-A.G.), with consensus assessment in diagnostically challenging cases.

EPs were classified according to the predominant histological pattern as functional, hyperplastic, fibrous, glandular, proliferative, adenomyomatous, or mixed. Morphological assessment included glandular crowding, cystic

glandular dilatation, gland-to-stroma ratio, fibrous core, thick-walled vessels, vascular proliferation, nuclear atypia, mitotic activity, and metaplastic changes. Background endometrium, when available, was classified as proliferative, secretory, hyperplastic, or disordered proliferative. Selective IHC assessment was performed in representative or diagnostically relevant cases, particularly in EPs showing increased architectural complexity, proliferative features, morphological heterogeneity, or cytological atypia. Ki-67 was used to assess epithelial proliferative activity, ER and PR to evaluate hormonal responsiveness, Bcl-2 to explore apoptotic regulation and cellular survival, p53 to assess tumor suppressor expression patterns, and PAX2 as a supportive marker of early premalignant glandular transformation.

IHC findings were interpreted in correlation with histopathological morphology and were used as complementary tools rather than standalone diagnostic criteria. Marker expression was assessed semiquantitatively according to staining distribution, intensity, cellular localization, and overall expression pattern.

Statistical analysis was performed using Python, version 3.11, with the SciPy statistical package. Categorical variables were expressed as absolute numbers and percentages. Comparisons between Group A and Group B were performed using the chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was used when expected frequencies were low. A p-value <0.05 was considered statistically significant. Continuous variables available only as summary descriptive data were reported descriptively and were not subjected to inferential testing. Given the retrospective observational design and moderate cohort size, the statistical analysis was considered exploratory and hypothesis-generating.

The study was conducted in accordance with the Declaration of Helsinki and institutional guidelines for research involving human subjects. Ethical approval was granted by the Ethics Committee of the University of Medicine and Pharmacy of Craiova, Romania (Approval No. 422/21 November 2025). All patients were evaluated according to institutional diagnostic and therapeutic protocols, and informed consent was obtained where applicable.

Results

The study cohort included 62 reproductive-aged women with histopathologically confirmed EPs, equally distributed between Group A (28-38 years, n=31) and Group B (39-49 years, n=31). The mean age was 38.5 years, and the mean BMI was 27.3 kg/m². Overall, 40.32% of patients were overweight and 35.48% were obese. Most patients were symptomatic (82.26%), whereas 17.74% were diagnosed incidentally during US or hysteroscopic evaluation. Abnormal uterine bleeding (AUB) was recorded in 66.13% of the cohort, while infertility history was present in 32.26% (Table 1).

Table 1. Baseline demographic and clinical characteristics of the patient cohort.

Characteristics	Patient cohort (n=62)
Age, mean (years)	38.5
Age range (years)	28-49
BMI (kg/m²), mean (range)	27.3 (24.8-33.9)
Normal weight	15 (24.19)
Overweight	25 (40.32)
Obesity	22 (35.48)
Nulliparous	9 (14.52)
Parity=1	35 (56.45)
Parity >1	18 (29.03)
Previous abortions	19 (30.65)
Previous cesarean section	23 (37.10)
Smoking	21 (33.87)
Infertility history	20 (32.26)
Symptomatic patients	51 (82.26)
Abnormal uterine bleeding	41 (66.13)
Incidental diagnosis	11 (17.74)

BMI, body mass index.

Clinical presentation varied substantially between the two age-defined groups. AUB increased from 41.94% in Group A to 90.32% in Group B ($p<0.001$), representing the strongest clinical difference identified in the study.

Irregular cycles were also more frequent in Group B (70.97% vs 48.39%), with a borderline intergroup difference ($p=0.070$). Incidental diagnosis increased from 9.68% to 25.81% ($p=0.096$), while infertility was recorded in 41.94% of Group B compared with 22.58% of Group A ($p=0.103$). Recurrent pregnancy loss, prolonged bleeding, dyspareunia, previous EPs, and recurrent EPs were also more frequent in the older subgroup. By contrast, dysmenorrhea predominated in Group A (58.06% vs 41.94%), while pelvic pain showed a similar distribution between groups (Table 2).

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Table 2. Age-stratified clinical characteristics of patients with endometrial polyps.

Clinical characteristics	Group A (n=31)	Group B (n=31)	Total cohort (n=62)	p-value
Symptomatic patients	24 (77.42)	27 (87.10)	51 (82.26)	0.319
Incidental diagnosis	3 (9.68)	8 (25.81)	11 (17.74)	0.096
Abnormal uterine bleeding (AUB)	13 (41.94)	28 (90.32)	41 (66.13)	<0.001
Infertility	7 (22.58)	13 (41.94)	20 (32.26)	0.103
Recurrent pregnancy loss (>2)	2 (6.45)	6 (19.35)	8 (12.90)	0.255
Intermenstrual bleeding (IMB)	9 (29.03)	10 (32.26)	19 (30.65)	0.783
Heavy menstrual bleeding (HMB)	3 (9.68)	4 (12.90)	7 (11.29)	1.000
Prolonged bleeding	6 (19.35)	9 (29.03)	15 (24.19)	0.374
Irregular cycles	15 (48.39)	22 (70.97)	37 (59.68)	0.070
Postcoital bleeding	5 (16.13)	4 (12.90)	9 (14.52)	1.000
Pelvic pain	10 (32.26)	9 (29.03)	19 (30.65)	0.783
Dysmenorrhea	18 (58.06)	13 (41.94)	31 (50.00)	0.204
Dyspareunia	4 (12.90)	7 (22.58)	11 (17.74)	0.319
Vaginal discharge	13 (41.94)	10 (32.26)	23 (37.10)	0.430
Anemia	5 (16.13)	3 (9.68)	8 (12.90)	0.707
Previous polyp	4 (12.90)	9 (29.03)	13 (20.97)	0.119
Recurrent polyp	0 (0.00)	3 (9.68)	3 (4.84)	0.238

AUB subtypes were not mutually exclusive; individual patients could present with multiple bleeding patterns.

The endocrine-metabolic profile also differed descriptively across reproductive age. Metabolic syndrome increased from 9.68% in Group A to 19.35% in Group B, while diabetes mellitus and insulin resistance each increased from 6.45% to 12.90%. Thyroid disorders were recorded in 12.90% of Group B compared with 3.23% of Group A. Progesterone therapy, intrauterine device use, and fertility treatment were also more frequent in Group B. Conversely, oral contraceptive use was more frequent in Group A (25.81% vs 9.68%, p=0.096), while PMOS/PCOS showed a comparable distribution between groups (Table 3).

Table 3. Age-stratified metabolic, endocrine, and hormonal profile of patients with endometrial polyps.

Hormonal and metabolic characteristics	Group A (n=31)	Group B (n=31)	Total cohort (n=62)	p-value
Metabolic syndrome	3 (9.68)	6 (19.35)	9 (14.52)	0.473
Diabetes mellitus	2 (6.45)	4 (12.90)	6 (9.68)	0.671
Arterial hypertension	1 (3.23)	3 (9.68)	4 (6.45)	0.612
Insulin resistance	2 (6.45)	4 (12.90)	6 (9.68)	0.671
PMOS/PCOS	6 (19.35)	5 (16.13)	11 (17.74)	0.740
Thyroid disorders	1 (3.23)	4 (12.90)	5 (8.06)	0.354
Hormonal therapy	1 (3.23)	2 (6.45)	3 (4.84)	1.000
Oral contraceptive use	8 (25.81)	3 (9.68)	11 (17.74)	0.096
Progesterone therapy	3 (9.68)	6 (19.35)	9 (14.52)	0.473
Intrauterine device (IUD)	1 (3.23)	5 (16.13)	6 (9.68)	0.195
Fertility treatment	3 (9.68)	6 (19.35)	9 (14.52)	0.473

PMOS, polyendocrine metabolic ovarian syndrome; PCOS, polycystic ovary syndrome.

Associated gynecological pathology was identified throughout the cohort, with leiomyomas representing the most frequent condition (27.42%). Their frequency increased from 22.58% in Group A to 32.26% in Group B.

Adenomyosis, endometriosis, EH, ovarian cysts, and ovarian tumors were also more frequent in Group B, while PCOS morphology remained similarly distributed across the two groups. EH was identified in 12.90% of Group B compared with 6.45% of Group A (Table 4).

Table 4. Age-stratified associated gynecological pathology in patients with endometrial polyps.

Associated gynecological pathology	Group A (n=31)	Group B (n=31)	Total cohort (n=62)	p-value
Adenomyosis	4 (12.90)	5 (16.13)	9 (14.52)	1.000
Endometriosis	3 (9.68)	4 (12.90)	7 (11.29)	1.000
Leiomyomas	7 (22.58)	10 (32.26)	17 (27.42)	0.393
Submucous leiomyoma	2 (6.45)	3 (9.68)	5 (8.06)	1.000
Intramural leiomyoma	5 (16.13)	6 (19.35)	11 (17.74)	0.740
Subserous leiomyoma	0 (0.00)	1 (3.23)	1 (1.61)	1.000
Cervical polyps	0 (0.00)	1 (3.23)	1 (1.61)	1.000
Ovarian cysts	2 (6.45)	3 (9.68)	5 (8.06)	1.000
Ovarian tumors	0 (0.00)	1 (3.23)	1 (1.61)	1.000
PCOS morphology	6 (19.35)	5 (16.13)	11 (17.74)	0.740
Endometrial hyperplasia (EH)	2 (6.45)	4 (12.90)	6 (9.68)	0.671

PCOS, polycystic ovary syndrome.

US assessment demonstrated a predominantly solitary lesion profile. Solitary EPs were identified in 74.19% of the cohort, compared with 25.81% multiple EPs. Mean maximal lesion diameter increased from 11mm in Group A to 14mm in Group B. Corporal location predominated overall (58.06%), followed by fundal (30.65%) and isthmic localization (11.29%). Regular contours were recorded in 80.65% of cases, although irregular contours increased from 12.90% in Group A to 25.81% in Group B. Heterogeneous morphology similarly increased from 32.26% to 48.39%, while heterogeneous background endometrium increased from 38.71% to 58.06%. Mean endometrial thickness increased from 7mm in Group A to 9mm in Group B. A feeding vessel was identified in 64.52% of cases, and a detectable vascular pattern was present in 58.06% (Table 5).

Table 5. Age-stratified ultrasonographic characteristics of endometrial polyps.

Ultrasonographic characteristics	Group A (n=31)	Group B (n=31)	Total cohort (n=62)	p-value
Solitary polyps	24 (77.42)	22 (70.97)	46 (74.19)	0.562
Multiple polyps	7 (22.58)	9 (29.03)	16 (25.81)	0.562
Polyp size, maximal diameter*, mm, mean (range)	11 (4-25)	14 (7-35)	12.5 (4-35)	-
Fundal location	12 (38.71)	7 (22.58)	19 (30.65)	0.168
Corporal location	17 (54.84)	19 (61.29)	36 (58.06)	0.607
Uterine isthmus	2 (6.45)	5 (16.13)	7 (11.29)	0.425
Regular contour	27 (87.10)	23 (74.19)	50 (80.65)	0.199
Irregular contour	4 (12.90)	8 (25.81)	12 (19.35)	0.199
Homogeneous morphology	21 (67.74)	16 (51.61)	37 (59.68)	0.196
Heterogeneous morphology	10 (32.26)	15 (48.39)	25 (40.32)	0.196
Feeding vessel	19 (61.29)	21 (67.74)	40 (64.52)	0.596
Detectable vascular pattern	17 (54.84)	19 (61.29)	36 (58.06)	0.607
Endometrial thickness, mm, mean (range)	7 (4-16)	9 (5-22)	8 (4-22)	-
Homogeneous endometrium	19 (61.29)	13 (41.94)	32 (51.61)	0.127
Heterogeneous endometrium	12 (38.71)	18 (58.06)	30 (48.39)	0.127
Hyperechoic lesions	17 (54.84)	16 (51.61)	33 (53.23)	0.799
Isoechoic lesions	2 (6.45)	1 (3.23)	3 (4.84)	1.000
Mixed echogenicity	12 (38.71)	14 (45.16)	26 (41.94)	0.607

Continuous variables reported as mean and range were analyzed descriptively only;
therefore, p-values were not calculated for these parameters.
*The maximal sonographic diameter (mm) measured in the plane of best lesion visualization.
In cases with multiple polyps, measurements were based on the dominant lesion.

Representative TVUS findings reflected the predominant solitary and vascularized profile of EPs in the cohort. The lesions showed corporal or fundal localization, regular to mildly irregular contours, predominantly homogeneous echotexture, well-defined margins, and preserved surrounding endometrial architecture.

Doppler assessment demonstrated a single or central feeding vessel with variable adjacent vascular signal (Figure 1,2).

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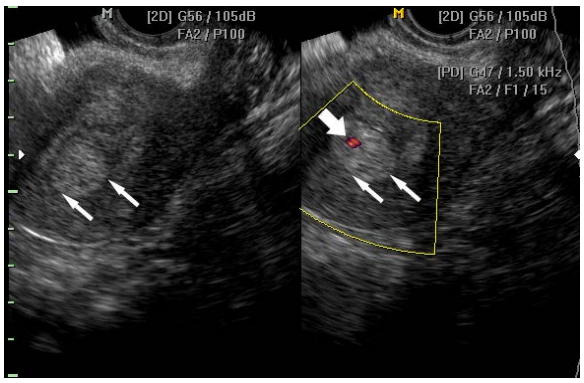


Figure 1. Dual sagittal TVUS image in a reproductive-aged woman, demonstrating a solitary corporal endometrial polyp (thin white arrows), with regular contour, homogeneous echotexture, smooth margins, and preserved surrounding endometrial architecture. Power Doppler demonstrates a single feeding vessel (thick white arrow).

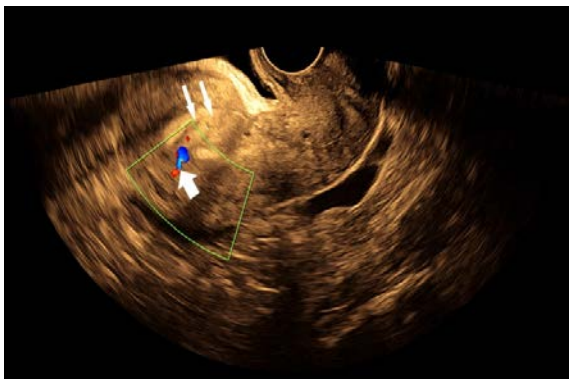


Figure 2. Sagittal TVUS image in a reproductive-aged woman, demonstrating a solitary fundal endometrial polyp (thin white arrows), with mildly irregular contour, homogeneous echotexture, and well-defined margins. Color Doppler demonstrates a central feeding vessel (thick white arrow) and detectable surrounding vascular signal.

The increase in mean lesion diameter in Group B was accompanied by a greater frequency of irregular contours, heterogeneous morphology, and heterogeneous surrounding endometrium. Larger fundal and fundocorporal EPs retained predominantly well-defined margins and relatively homogeneous echotexture, while Doppler assessment demonstrated prominent or central feeding vessels, marked lesion vascularity, and detectable adjacent vascular signals (Figure 3,4).

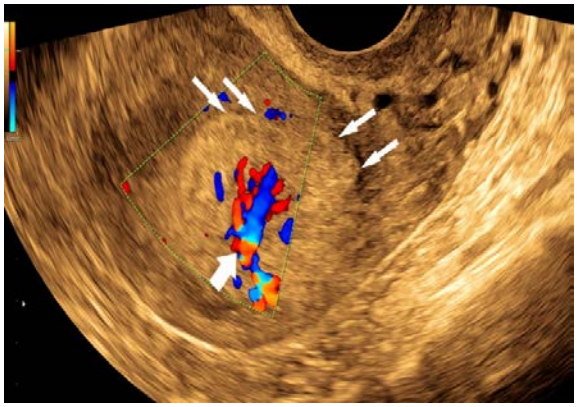


Figure 3. Sagittal TVUS image in a reproductive-aged woman, demonstrating a large solitary fundal endometrial polyp (thin white arrows), with regular contour, relatively homogeneous echotexture, smooth margins, and relatively homogeneous surrounding endometrial architecture. Color Doppler HD flow demonstrates a prominent feeding vessel (thick white arrow) with marked vascularity and detectable vascular pattern.

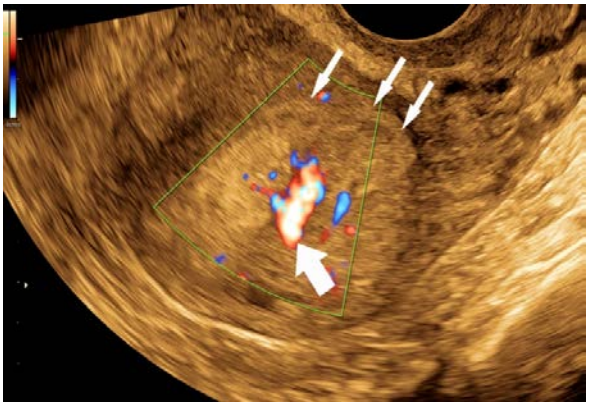


Figure 4. Sagittal TVUS image in a reproductive-aged woman, demonstrating a solitary fundocorporal endometrial polyp (thin white arrows), with regular contour, relatively homogeneous echotexture, smooth margins, and relatively homogeneous surrounding endometrial architecture. Color Doppler demonstrates a central feeding vessel (thick white arrow) with detectable adjacent vascular signal.

Histopathological assessment subsequently defined the tissue substrate of the clinical and US heterogeneity, including subtype distribution, glandular architecture, cytological features, stromal-vascular remodeling, and background endometrial patterns across the two groups (Table 6).

Table 6. Age-stratified histopathological characteristics of endometrial polyps.

Histopathological characteristics	Group A (n=31)	Group B (n=31)	Total cohort (n=62)	p-value
Functional polyps	10 (32.26)	4 (12.90)	14 (22.58)	0.068
Hyperplastic polyps	2 (6.45)	4 (12.90)	6 (9.68)	0.671
Fibrous polyps	2 (6.45)	3 (9.68)	5 (8.06)	1.000
Glandular polyps	5 (16.13)	2 (6.45)	7 (11.29)	0.425
Proliferative polyps	4 (12.90)	2 (6.45)	6 (9.68)	0.671
Adenomyomatous polyps	1 (3.23)	3 (9.68)	4 (6.45)	0.612
Mixed subtype	7 (22.58)	13 (41.94)	20 (32.26)	0.103
Glandular crowding	9 (29.03)	17 (54.84)	26 (41.94)	0.039
Cystic glandular dilatation	8 (25.81)	14 (45.16)	22 (35.48)	0.111
Increased gland-to-stroma ratio	9 (29.03)	13 (41.94)	22 (35.48)	0.288
Fibrous core	17 (54.84)	20 (64.52)	37 (59.68)	0.437
Thick-walled vessels	16 (51.61)	18 (58.06)	34 (54.84)	0.610
Vascular proliferation	9 (29.03)	12 (38.71)	21 (33.87)	0.421
Nuclear atypia	2 (6.45)	5 (16.13)	7 (11.29)	0.425
Mitotic activity	8 (25.81)	10 (32.26)	18 (29.03)	0.576
Metaplastic changes	4 (12.90)	5 (16.13)	9 (14.52)	1.000
Proliferative endometrium	17 (54.84)	12 (38.71)	29 (46.77)	0.203
Secretory endometrium	5 (16.13)	4 (12.90)	9 (14.52)	1.000
Hyperplastic endometrium	3 (9.68)	5 (16.13)	8 (12.90)	0.707
Disordered proliferative endometrium	6 (19.35)	10 (32.26)	16 (25.81)	0.246

Histological subtype classification was based on the predominant morphological pattern of each lesion and was considered mutually exclusive. Polyps exhibiting substantial overlap between two or more histological patterns were categorized as mixed subtype. Background endometrium was classified according to the predominant histological pattern and considered mutually exclusive.

Mixed subtype represented the most frequent histological category overall (32.26%), followed by functional EPs (22.58%).

Functional EPs predominated in Group A (32.26% vs 12.90%), with a borderline intergroup distribution (p=0.068), whereas mixed subtype increased from 22.58% in Group A to 41.94% in Group B (p=0.103).

Hyperplastic, fibrous, and adenomyomatous EPs were also more frequent in Group B.

Glandular crowding was the principal histopathological discriminator between groups, increasing from 29.03% in Group A to 54.84% in Group B (p=0.039).

Cystic glandular dilatation also increased from 25.81% to 45.16% (p=0.111), while increased gland-to-stroma ratio rose from 29.03% to 41.94%. Fibrous core and thick-walled vessels were the most frequent structural features overall, being recorded in 59.68% and 54.84% of cases, respectively. Nuclear atypia increased from 6.45% to 16.13%, and mitotic activity from 25.81% to 32.26%. Hyperplastic and disordered proliferative background endometrium were more frequent in Group B, whereas proliferative endometrium predominated in Group A.

Hyperplastic changes without atypia were characterized by mildly to moderately crowded, variably dilated glands with irregular contours, cytologically bland epithelium, preserved nuclear polarity, and abundant intervening stroma (Figure 5,6).

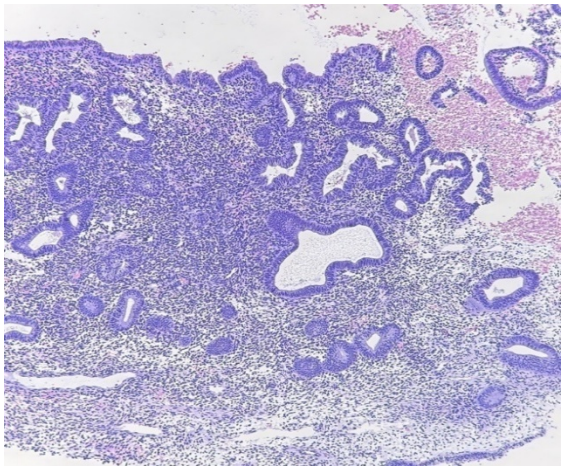


Figure 5. Endometrial polyp with hyperplastic changes without atypia, showing mildly to moderately crowded, variably dilated glands with irregular contours, cytologically bland epithelium, preserved nuclear polarity, and abundant intervening stroma. No features of atypical EH/endometrial intraepithelial neoplasia are identified. Hematoxylin-eosin staining, ×100.

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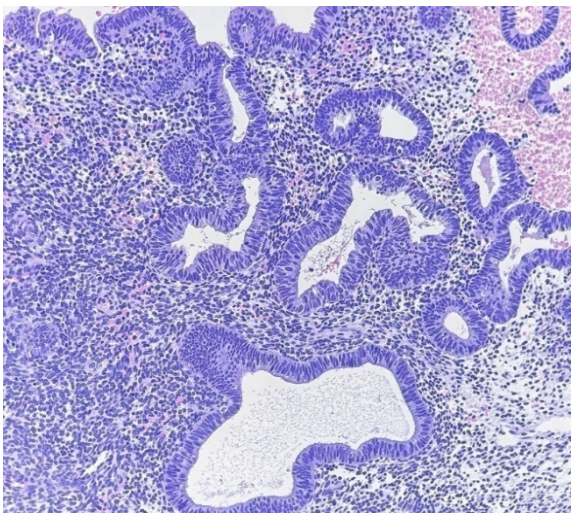


Figure 6. High-amplification view of the same endometrial polyp with hyperplastic changes without atypia, showing mildly crowded, variably dilated glands lined by cytologically bland epithelium. No architectural complexity or nuclear atypia diagnostic of atypical EH/endometrial intraepithelial neoplasia is identified. Hematoxylin-eosin staining, ×200.

By contrast, EPs with cytological atypia showed relatively crowded glands with irregular contours and focal cyto-nuclear abnormalities, without significant architectural complexity or solid growth (Figure 7,8

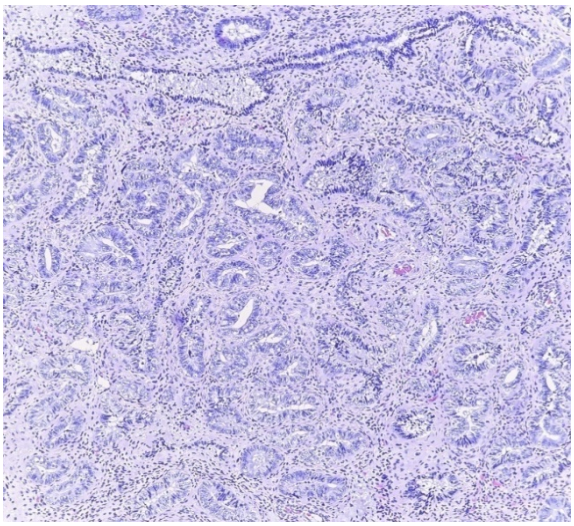


Figure 7. Endometrial polyp with hyperplastic changes and cito-nuclear atypia, showing relatively crowded glands with irregular contours, scattered within a fibrous stroma with hyalinized vessel walls. Hematoxylin-eosin staining, ×100.

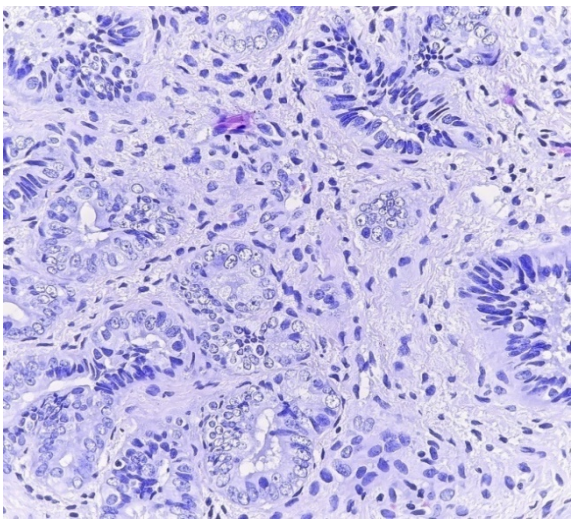


Figure 8. High-amplification view of the same endometrial polyp with hyperplastic changes and at least focal cyto-nuclear atypia, showing relatively crowded glands lined by columnar epithelium with vesicular or hyperchromatic nuclei. No significant architectural complexity or solid areas are identified. Hematoxylin-eosin staining, ×400.

IHC assessment provided complementary biological information in representative lesions.

Loss of nuclear PAX2 expression was identified in the glandular epithelium, while Ki-67 demonstrated a high and heterogeneous proliferative index in corresponding areas (Figure 9,10).

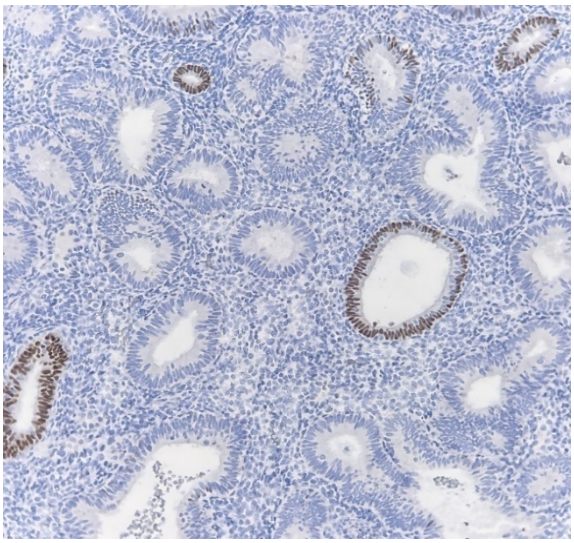


Figure 9. Endometrial polyp showing loss of nuclear PAX2 expression in the glandular epithelium. PAX2 immunostaining, ×200.

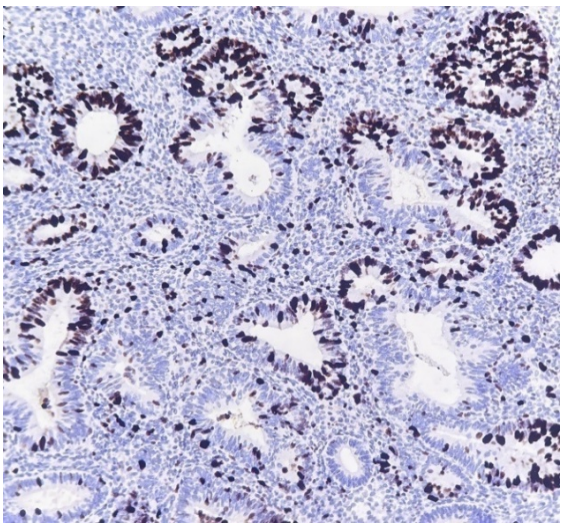


Figure 10. Endometrial polyp showing a high Ki-67 proliferative index, with a heterogeneous nuclear staining in various areas of the glandular epithelium. Ki-67 immunostaining, ×200.

Overall, the integrated clinical, US, histopathological, and selective IHC assessment identified an age-associated pattern within the reproductive period. Group B was characterized by a markedly higher frequency of AUB and significantly greater glandular crowding, together with higher frequencies of irregular cycles, infertility, incidental diagnosis, mixed histological subtypes, larger lesions, increased endometrial thickness, and more heterogeneous US and background endometrial profiles. Loss of PAX2 expression and a high, heterogeneous Ki-67 proliferative index were documented in representative lesions. Taken together, these findings support the heterogeneity of EPs and indicate that their clinical expression, imaging morphology, and tissue architecture may vary across reproductive age, providing the basis for further interpretation in relation to hormonal exposure, metabolic context, endometrial remodeling, and biological behavior.

Discussion

The present study supports the concept that EPs are heterogeneous proliferative lesions whose clinical expression, US appearance, and histopathological architecture vary across reproductive age. The clearest age-associated differences were the marked increase in AUB and the significantly greater frequency of glandular crowding in Group B. These were accompanied by higher frequencies of irregular cycles, infertility, incidental diagnosis, mixed histological subtypes, cystic glandular dilatation, larger lesions, increased endometrial thickness, and more heterogeneous lesion and background endometrial morphology. Although several differences were descriptive or borderline, their convergence suggests progressive endometrial remodeling rather than a uniform effect of chronological age alone. Current guidance similarly supports integrating clinical presentation, imaging, hysteroscopic assessment, and histopathological confirmation when evaluating EPs [21].

Hysteroscopy remains central because it permits direct visualization, targeted removal, and improved sampling compared with blind procedures [22].

AUB was the dominant clinical discriminator, increasing from 41.94% in Group A to 90.32% in Group B. This reinforces the need to investigate focal intracavitary pathology in reproductive-aged women with abnormal bleeding while maintaining a structured differential diagnosis that includes structural and nonstructural causes [23].

Infertility affected nearly one-third of the cohort and was more frequent in Group B. EPs may impair endometrial receptivity through mechanical interference and local molecular or inflammatory changes, supporting individualized hysteroscopic polypectomy in selected infertile women [24].

Previous and recurrent EPs were also more frequent in the older group, consistent with evidence that recurrence may be influenced by lesion multiplicity, hormonal exposure, metabolic context, and completeness of removal [25].

The predominantly overweight-obese profile of the cohort provides an additional biological framework. Adiposity and insulin resistance may promote prolonged estrogenic stimulation and altered endometrial homeostasis. Weight gain and metabolic dysfunction are particularly relevant in women with PMOS/PCOS [20,26,27], which has also been associated with an increased risk of premalignant and malignant changes within EPs [28].

In the present cohort, however, PMOS/PCOS prevalence was comparable between groups, indicating that the observed age-associated differences cannot be attributed to this condition alone.

US findings showed that a typical EP pattern does not exclude substantial variability. Most lesions were solitary, regularly contoured, and corporal, and a feeding vessel was identified in approximately two-thirds of cases. Group B nevertheless showed larger lesions and higher frequencies of irregular contours, heterogeneous morphology, and heterogeneous background endometrium. These observations support

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combined interpretation of lesion morphology, location, vascularity, and surrounding endometrial appearance rather than reliance on endometrial thickness alone [29].

Accurate lesion delineation is also important for selecting the appropriate hysteroscopic technique and achieving complete excision [30].

Endometrial thickness should be interpreted according to age, reproductive status, symptoms, and focal morphology, as its diagnostic value varies across clinical settings [31].

Histopathology provided the structural substrate of the observed heterogeneity. EP development appears to involve altered hormonal responsiveness, apoptosis, angiogenesis, stromal remodeling, and local inflammatory pathways [32].

Direct hysteroscopic visualization may improve clinicopathological correlation by enabling targeted sampling of heterogeneous areas [33], while office-based and operating-room approaches should be individualized according to lesion characteristics, patient tolerance, and procedural complexity [34].

Histopathological confirmation remains essential because apparently benign EPs may contain hyperplastic, atypical, or malignant foci. Although malignant transformation is uncommon in reproductive-aged women, age, menopausal status, AUB, lesion characteristics, and metabolic comorbidity remain relevant risk modifiers [35-38].

Background endometrium also contributed to biological interpretation. Proliferative endometrium predominated in Group A, whereas hyperplastic and disordered proliferative patterns were more frequent in Group B, supporting assessment of both the lesion and surrounding endometrium [39].

Glandular crowding, the principal histopathological discriminator, should not be equated with atypical hyperplasia or endometrioid intraepithelial neoplasia in isolation, but it warrants careful architectural and cytological evaluation. Mutant clones may occur in morphologically unremarkable endometrium [40], and combined loss of PAX2 and PTEN has been associated with premalignant progression [41].

Diagnostic interpretation remains challenging because architectural complexity, cytological atypia, metaplastic change, and sampling limitations may reduce reproducibility [42].

In difficult cases, panels incorporating PAX2, PTEN, and beta-catenin may provide supportive evidence [43], but biomarkers must remain subordinate to morphology and clinical context [44].

The IHC component was intended to complement routine histopathology. Loss of PAX2 expression and a high, heterogeneous Ki-67 proliferative index were documented in representative lesions, while detailed ER, PR, Bcl-2, and p53 findings were not available for comparative quantitative analysis. Aberrant p53 and high Ki-67 expression may characterize aggressive or non-endometrioid proliferations involving EPs [45-47].

Study strengths include the multicenter design, equal age-group distribution, integrated clinical, US, and pathological assessment, and detailed histological characterization.

Limitations include the retrospective design, moderate cohort size, descriptive analysis of continuous variables, variation in sampling methods, and selective rather than cohort-wide standardized IHC. Given these methodological considerations, the present findings are best interpreted as exploratory and hypothesis-generating, while supporting a broader integrated framework for EP assessment and providing a rationale for larger prospective studies incorporating standardized hysteroscopy, lesion-oriented sampling, quantitative IHC, molecular profiling, and longitudinal follow-up.

Conclusions

EPs in reproductive-aged women exhibited a clear age-associated clinicopathological heterogeneity.

Later reproductive age was associated with a more pronounced symptomatic profile, greater glandular architectural complexity, larger and more heterogeneous lesions, and more frequent alterations of the background endometrium.

Collectively, these findings support the view that EPs represent a biologically and morphologically heterogeneous spectrum of focal endometrial proliferative lesions, with measurable variation across the reproductive-age continuum.

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None to declare.

Author Contributions

Conceptualization, V.T.M. and C.B.; Methodology, V.T.M., R.G.C., N.D.O., A.C.C. and C.B.; Investigation, V.T.M., M.O., T.-A.G., A.C.C., S.P., A.V.T. and C.B.; Data analysis, R.G.C., A.C.C., S.P., and A.V.T.; Manuscript writing and initial draft preparation, V.T.M., R.G.C., N.D.O., S.P., N.-L.V.; Manuscript review and editing, M.O., A.C.C. and C.B.; Supervision, C.B.

All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted in accordance with the Declaration of Helsinki; the study and the protocols utilized therein were approved by the Institutional Ethics Committee of University of Medicine and Pharmacy Craiova, 422/21.11.2025.

Consent Statement

All patients were evaluated according to institutional diagnostic and therapeutic protocols, and informed consent was obtained where applicable.

Data availability

All data presented in the manuscript are available from the authors upon request.

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