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Endometrial Hyperplasia on Rising Trends among Peri-Menopausal Women

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ABSTRACT

Endometrial hyperplasia demonstrates a uterine pathology characterized by a range of endometrial morphological remodeling. The clinical importance of endometrial hyperplasia lies in its progression to endometrial carcinoma. **Objectives:** To analyze histopathological findings of endometrial biopsy in perimenopausal women having abnormal uterine bleeding and to observe the correlation of various risk factors with endometrial hyperplasia. **Methods:** The cross-sectional study was conducted at the Department of Gynaecology, Nishtar Medical University, Pakistan. Two hundred and fifty-five perimenopausal women having abnormal uterine bleeding of 3-12 months' duration were included. The participants were subjected to histopathological analysis of endometrial biopsy obtained by dilatation and curettage. All the information and the histopathology report were entered on a specific proforma. Data analysis was performed using SPSS software version 26.0. **Results:** Out of a total of 255 patients, the mean age was 48+/-6 years. A vast majority was grand multiparous (n=163, 64%). Out of a total of 255 endometrial samples, the majority (n=88, 34.5%) turned out to be proliferative endometrium, indicating hormonal imbalance like unopposed estrogen stimulation. In total, 66 (25.9%) samples fulfilled the criteria of endometrial hyperplasia. 54 (21.7%) had endometrial hyperplasia without atypia, while 12 (4.2%) had atypical endometrial hyperplasia. Regarding atypical uterine bleeding, the commonest symptom was heavy regular cycle (n=74, 29%) followed by irregular vaginal bleeding (n=70, 27.5%). **Conclusions:** It was concluded that atypical uterine bleeding in the peri-menopausal life period is alarming. All such women should undergo endometrial histopathological examination to detect endometrial hyperplasia to prevent its progression to endometrial carcinoma.

INTRODUCTION

The endometrium corresponds to the innermost layer of the uterus, which undergoes a series of cyclical changes during the menstrual cycles of a woman's reproductive years. This takes place due to a complex display between two hormones, namely estrogen and progesterone. The estrogen causes cellular proliferation of the endometrium, leading to uterine wall thickness, while progesterone causes cellular differentiation in the endometrium. If the equilibrium between the intricate display of the two hormones is disturbed, it results in chronic estrogenic stimulation of endometrium, unopposed by progesterone, leading to the marked thickness of the uterine wall [1]. Endometrial hyperplasia (EH) corresponds to a uterine pathology characterized by a range of morphological changes in the endometrium. The hallmark of EH is an exacerbation of the endometrial gland-to-stroma ratio in comparison to normal proliferative endometrium [2]. EH mostly presents with abnormal uterine bleeding. It may be in the form of heavy menstrual bleeding, inter-menstrual bleeding, postmenopausal bleeding, irregular bleeding or unexpected bleeding on hormone replacement therapy. It is estimated that EH is responsible for 15% of post-menopausal bleeding [3]. The ultimate diagnosis of endometrial hyperplasia is based on histopathological evaluation of the endometrium. The endometrial specimen can be obtained by Pipelle sampling, endometrial curettage, or hysteroscopic guided endometrial sampling. EH is a non-physiological, non-invasive precursor of endometrial carcinoma. According to the World Health Organization, there are two types of EH: EH without atypia

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and atypical EH [4]. The anticipated risk of progression to endometrial carcinoma is much more frequent with atypical hyperplasia as compared to EH without atypia. So far, studies have revealed that endometrial cancer is the most common gynaecological malignancy prevailing in developed countries and second only to cervical carcinoma when estimated worldwide [5, 6]. The prevalence rate is 21% for endometrial hyperplasia in Pakistan, while it is 20.3% in Iran [7, 8]. Endometrial hyperplasia, a precursor of endometrial carcinoma, is of great clinical significance, and its detection can provide opportunities to prevent endometrial carcinoma [9]. The causative factors leading to endometrial hyperplasia are the same as those for endometrial carcinoma. These include increased body mass index with excessive adipose tissue conversion of androgens to estrogen, polycystic ovary syndrome with associated anovulation, estrogen replacement therapy, or estrogen-secreting tumor. Obesity is specifically considered the strongest risk factor for EH and endometrial carcinoma. Endometrial carcinoma is three times more common in obese or overweight women, and the risk increases by 50% for every 5 units of body mass index (BMI) increase [10]. The prevalence of endometrial carcinoma has surged in recent years, partially due to rising trends of obesity and also due to changes in female reproductive patterns [11]. Endometrial carcinoma has historically been considered a disease of post-menopausal age group. Owing to increasing trends of obesity in women, we are observing a shift of rising trends of EH and consequent EC in pre- and peri-menopausal age group [12]. The importance of pre-cancer detection and patient risk stratification cannot be overlooked and is the key to the detection and prevention of cancer. Currently, no screening test is available for endometrial carcinoma [13]. Despite the increasing frequency of EH, there is scanty awareness among the general population and little or no local research work as compared to its social burden.

This study aims to analyze histopathological findings of endometrial biopsy in peri-menopausal women having abnormal uterine bleeding and to observe the correlation of various risk factors with EH. Consequently, we explored the prevalence of EH in peri-menopausal women so that measures can be taken to prevent its progression to endometrial malignancy.

METHODS

This cross-sectional study was conducted in the Department of Gynaecology, Nishtar Medical University, Pakistan from July 2023 to June 2024. Ethical approval was granted by the Institutional Ethical Review Board vide letter number (18675) to conduct this study. The sample size was calculated using the WHO sample size calculator using the formula, n=E2Z2.P.(1-P).The primary outcome variable for sample size calculation was the prevalence of endometrial hyperplasia among peri-menopausal women having atypical uterine bleeding in a similar population. It was set at 21% based on prior studies [7]. Non-probability consecutive sampling was used. A total of 255 perimenopausal women in the age range of 40-55 years, having abnormal uterine bleeding spanning 3-12 months' duration, were included in the study. Women with bleeding disorders like von Willebrand disease, Idiopathic Thrombocytopenic Purpura, and taking drugs like warfarin and aspirin were excluded. Hypothyroidism, pelvic inflammatory disease, fibroid, polyp, and cervical pathology (cervical polyp, cervicitis) were also excluded factors. Informed consent was obtained from patients regarding their inclusion in the study. They were ensured regarding confidentiality and the fact that there was no anticipated risk involved to the patient while participating in the current study. A detailed history was inquired and participants were subjected to endometrial sampling (both outpatient clinic procedures and inpatient procedures under anesthesia). The sample was preserved in 10% Formalin solution. The consultant pathologists performed the histopathological analysis based on morphometric study and standard WHO criteria. A structured proforma was used to gather all the information, including demographic details (age, BMI), clinical history (bleeding pattern, parity, history of diabetes mellitus, hormonal intake or polycystic ovaries), and histopathological findings. Data analysis was accomplished by using SPSS software version 26.0. The primary outcome variable was the presence or absence of EH. The secondary variables were age, parity, BMI history of diabetes mellitus, polycystic ovaries, or hormonal intake. Frequency and percentages were calculated for these variables. A chi-square test was used to calculate the significance of the test. A p-value <0.05 was taken as significant.

RESULTS

Among the total 255 patients, the mean age was 48 ± 6 years. A vast majority were multiparous (n=210, 84.4%) and obese (n=133, 52.2%). Out of all those, 32 (12.5%) had Diabetes Mellitus, and 79 (31%) were also diagnosed to have polycystic ovaries (Table 1).

Table 1: Correlation of Various Characteristics with Endometrial Hyperplasia

Characteristics		Frequency (%)	p-value
Age (Years)	40-45	82 (32.1%)	0.615
	45-50	141 (55.3%)	
	50-55	32 (12.5%)	
Parity	Nullipara	40 (15.6%)	0.024
	Multipara1-4	52 (20.4%)	
	Grand Multipara >4	163 (64%)	

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BMI (Kg/m^2)	18.5-24.9	48(18.8%)	<0.001
	25-29.9	74 (29%)	
	30 or More	133 (52.2%)	
Diabetes Mellitus	Yes	32 (12.5%)	<0.001
	No	223 (87.5%)	
Polycystic Ovaries	Yes	79 (31%)	<0.001
	No	176 (69%)	
History of Hormonal Intake	Yes	34 (13.3%)	--
	No	221 (86.7%)	

Regarding abnormal/atypical uterine bleeding, the commonest symptom was heavy regular cycle (n=74, 29%) followed by irregular vaginal bleeding (n=70, 27.5%) (Table 2).

Table 2: Pattern of Abnormal Uterine Bleeding

Pattern of Abnormal or Atypical Bleeding	Frequency (%)
Regular Heavy Menstruation	74 (29%)
Frequent Heavy Menstruation	43 (16.9%)
Irregular Menstruation	70 (27.5%)
Infrequent Menstruation	21 (8.2%)
Continuous Vaginal Bleeding	47 (18.4%)

Out of a total of 255 endometrial samples, the majority (n=88, 34.5%) turned out to be proliferative endometrium, indicating hormonal upset like unopposed estrogen stimulation. In total, 66 (25.9%) samples fulfilled the criteria of endometrial hyperplasia. 54 (21.2%) had EH without atypia, while 12 (4.7%) had atypical EH (Table 3).

Table 3: Histological Findings in Endometrial Sample

Histological Finding	Frequency (%)
Proliferative Endometrium	88 (34.5%)
Secretory Endometrium	55 (21.6%)
Fibroids	25 (9.8%)
Polyps	14 (5.5%)
Endometrial Hyperplasia without Atypia	54 (21.2%)
Atypical Endometrial Hyperplasia	12 (4.7%)
Endometrial Carcinoma	7 (2.7%)

Out of total 66 EH histopathological reports, 42(63.6%) were obese and 43(65.1%) had polycystic ovaries (Table 4).

Table 4: Correlation Between Endometrial Hyperplasia and Contributing Factors

Characteristics		Histopathology of EH:n-66 (%)	p-value
BMI (Kg/m^2)	18.5-24.9	6 (9.1%)	0.026
	25-29.9	18 (27.3%)	
	30 or More	42 (63.6%)	
Diabetes Mellitus	Yes	22 (33.3%)	0.00026
	No	44 (66.7%)	
Polycystic Ovaries	Yes	43 (65.1%)	0.00094
	No	23 (34.8%)	

DISCUSSION

Perimenopause is the time interval that encompasses the final years of a woman's reproductive life. It is the period that commences in the early years after 40 and lasts for almost two years after the final menstrual cycle. It is accompanied by the symptoms of declining ovarian function. Abnormal uterine bleeding is the hallmark of this transitional phase. It is a wide-ranging phrase used to narrate irregularities in the menstrual cycle that may imply frequency, regularity, duration frequency, regularity, duration, and volume of flow and has negative repercussions on the quality of life. A total of 255 women with abnormal uterine bleeding after the age of 40 years were subjected to endometrial sampling. The histopathology report revealed EH in 25.9% of the cases. This result is quite high when we compare it with the study conducted by Bakos *et al.* almost 25 years ago when it was found to be around 12% [14]. In current study, EH without atypia was observed in 54 (21.2%) cases. This is quite close to that appraised by Munir S (21%) in a study conducted in Pakistan [7]. Another study conducted by Bakos *et al.*, in Pakistan yielded similar results (21%) [15]. The closer findings obtained can be explained by the fact that the inclusion criteria for the participants were almost alike, and the diagnostic modality used in these studies was similar, i.e., diagnostic curettage. These figures are quite high when we take a glance at a study conducted by Takreem *et al.* in Pakistan almost 15 years ago when endometrial hyperplasia incidence was reported to be 13% [16]. The recent rise in endometrial hyperplasia is largely linked to changing lifestyles, including junk food and lack of physical activity, leading to obesity, polycystic ovarian syndrome, and eventual endometrial hyperplasia. Qureshi *et al.*, from India, reported an incidence of 33%, higher than current findings [17]. This variation might be due to the reason that they conducted a study on those patients who underwent hysterectomy. This provides the opportunity for visual analysis of the whole specimen and biopsy of grossly suspected areas, resulting in higher detection rates. In present study, atypical hyperplasia was observed in 12 (4.7%) cases. However, a similar study conducted in India reported that the incidence of atypical hyperplasia was 5.4% [18, 19]. The high rates in the later studies might result from hysteroscopic guided endometrial sampling in most cases, as it allows a more accurate selection of unhealthy-looking areas for biopsy. The incidence observed is quite high compared with the 0.4% found in the study conducted by Jetley almost 10 years back [20]. In current study, endometrial carcinoma was eminent in 7 (2.7%) cases. The equivalent (2%) was observed by Masood *et al.*, [21] and Manzoor *et al.*, [22]. The most common risk factor for EH is obesity. In present study, 63.6 % of those diagnosed with

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EH were obese, while polycystic ovaries were detected in 65.1% of current cases. It is quite high when compared to that calculated by Wang *et al.*, (35%) [23]. Chi-square crosstab analysis yielded a p-value<0.05 for obesity, diabetes mellitus and polycystic ovaries, indicating a strong association. Both obesity and polycystic ovaries result in unopposed estrogen leading to endometrial hyperplasia. The tendency of obesity is rising trends due to the overwhelming use of junk food along with cola drinks and a sedentary lifestyle. This can be self-explanatory regarding the risk of endometrial hyperplasia in the current study. The development of validated and non-invasive diagnostic methods for early detection of endometrial hyperplasia may reduce the need for invasive procedures and facilitate timely treatment. The current guidelines provide a framework for managing endometrial hyperplasia in perimenopausal women, but ongoing research is essential to refine these recommendations and enhance patient care.

CONCLUSIONS

It was concluded that in the peri-menopausal age group, AUB should be considered, and endometrial sampling must be performed to rule out endometrial hyperplasia or endometrial malignancy. As obesity and polycystic ovaries are consistently being increased, so are the rising trends of endometrial hyperplasia. Time is needed to implement targeted public health interventions. Timely diagnosis can enable the patients to have surveillance or treatment, thus preventing future endometrial carcinoma development. Future research should explore innovative diagnostic tools and preventive strategies to manage this growing health challenge

Authors Contribution

Conceptualization: ST
Methodology: ST, FS
Formal analysis: ST, AA, FS
Writing review and editing: ST, AA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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