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Pathological findings following hysterectomy in women 45 years and older, and their relationship to menopausal status

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ABSTRACT

Background: Menopause is the physiological cessation of the reproductive cycle in elderly women; hysterectomy is surgical removal of the uterus and cervix. It was hypothesized that older premenopausal and postmenopausal women experienced different pathological findings following hysterectomies. To identify common pathological findings in hysterectomy specimens of women 45 years of age and older, and to correlate these findings with the women's menopausal status.

Methods: This cross-sectional study was conducted at the Histopathology Department of Dow international Medical College, Dow University of Health Sciences. Data of the hysterectomy specimens of women 45 years and older, reported during the three years from 2018-2020, were reviewed from the pathology reports and analyzed using SPSS (IBM v26).

Results: There were 525 hysterectomy samples from women 45 years of age and older. The mean age was 52.40 (±7.89) years; 236 (44.95%) of the women were postmenopausal, 207 (39.42%) were premenopausal, menopausal status was not known for 82 (15.62%). Abnormal uterine bleeding was the most frequent clinical presentation, reported in 256 (48.76%) women. Common benign uterine pathologies included leiomyomata and adenomyosis in 350 (66.67%) of the women, endometrial atrophy in 114 (21.71%), uterovaginal prolapse in 104 (20.0%), and endometrial polyp in 97 (18.48%) of the women. Endometrioid carcinoma of the endometrium affected 23 (4.38%) women, and serous carcinoma of the ovary involved 10 (2.50%). Endometrial atrophy (Fisher exact, p=0.00001), uterine prolapse ($\chi 2$, p=0.00001), endometrial cancer (Fisher exact, p=0.0002), ovarian cancer (Fisher exact, p=0.0008) and tubal cancer (Fisher exact, p=0.015) were significantly associated with postmenopausal women, whereas leiomyoma and adenomyosis had a higher frequency in premenopausal women ($\chi 2$, p=0.00001).

Conclusion: Most common pathological findings were leiomyomata and adenomyosis in premenopausal women. Endometrial atrophy and uterine prolapse in postmenopausal women. There was a significant association between postmenopausal status and endometrial, ovarian, and tubal malignancies.

Key Words: Hysterectomy, Pathology, Leiomyoma, Adenomyosis, Carcinoma Endometrium, Carcinoma Cervix, Uterine prolapse.

Introduction

Hysterectomy is the surgical removal of the uterus and cervix. Hysterectomy may be accompanied by unilateral or bilateral salpingo-oophorectomy, which is the removal of one sided or both sided fallopian tubes and ovaries.[1] Women of various ages undergo hysterectomies, however the reasons for the procedure vary in different age groups.

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Most often it is performed as a treatment for heavy and abnormal uterine bleeding, uterine prolapse, and benign and malignant uterine tumors.[2]

Menopause is a natural condition that marks the end of the reproductive cycle, when there is loss of follicular function, anovulation and significant reduction in the ovarian production of estrogen and progesterone. A woman is said to be in menopause when there is no menstruation for 12 consecutive months, it usually occurs between 45-55 years of age.[3] Decreased estrogen levels are responsible for the symptoms of hot flashes, mood swings, body ache, tiredness, sleep disturbances and decreased libido. Declining progesterone levels cause irregular menstrual cycles, abnormal uterine bleeding (AUB) which may be heavy or light, and frequent.[4] Aging is associated with a decline in physical function, which

may be accelerated by menopause. Oophorectomy with the hysterectomy leads to loss of estrogen and immediate menopause.[5] In the United States, a decreasing trend has been noted in hysterectomy and oophorectomy from 2005-2013, however compared to younger women, those above 55 years are more likely to undergo oophorectomy with the hysterectomy.[5] Women with hysterectomy with and without oophorectomy are at an increased risk of substantial physical limitations compared to the age-matched women without hysterectomy.[6]

Objective: To identify the common pathologies in the uterus and ovaries which led to hysterectomy in older women, who were either perimenopausal or had reached their physiological menopause; and to observe differences between the pathological findings in the premenopausal and postmenopausal women?

Methods

This cross-sectional study was conducted in the Department of Histopathology, Dow international Medical College, Dow University of Health Sciences. Approval from the Institutional Review Board was acquired (IRB-2099/DUHS/Approval/2021 dated 09-08-2021). The study was conducted from January 2021 till September 2021. Histopathology reports of all the hysterectomy specimens reported from January 2018 till December 2020 were evaluated from the compiled hard copies. Hysterectomy specimen of women 45 years and above were included, whereas, obstetric hysterectomies and those belonging to women less than 45 years were excluded. Data were entered and analyzed in Statistical Package for Social Sciences (SPSS, IBM version 26). Frequencies were calculated for the variables: clinical presentation, type of hysterectomy surgery, salpingo-oophorectomy, and the histopathological findings in the endometrium, myometrium, cervix, ovaries, and fallopian tubes. Based upon the clinical information, women were categorized into three menopausal categories: Premenopausal, postmenopausal and menopausal status not known, and were further stratified into 5 years' age groups. Frequencies and percentages of the three categories of women in each age group were calculated. The differences in the pathological findings in the hysterectomies between the premenopausal and postmenopausal categories were determined, after excluding the women whose menopausal status was not known. Pearson's Chi square and Fisher exact tests were applied, with a confidence interval of 95% and level of significance of 0.05.

Results

Over the course of the three years, 525 hysterectomy samples from women who were 45 years or older were received. Abdominal hysterectomy was performed in 432 (82.28%) patients, vaginal hysterectomy in 88 (16.76%) and supracervical hysterectomy in 5 (0.95%). Oophorectomy was performed in 400 patients (76.19%) and it was bilateral in 381 (72.57%). Mean age of the patients was 52.40 years (±7.89 SD). The foremost clinical symptoms identified from the clinical history were related to abnormal uterine bleeding (AUB) in 256 (48.76%) women, of these post-menopausal bleeding (PMB) was present in 58 (11.05%). Symptoms related to uterine prolapse were recorded in 104 (19.81%), and those related to abdominal mass or pain in 90 (17.14%) women.

The pathological findings in the endometrium are listed in Table I.

Table I: Pathological findings in the endometrium (Hysterectomy, n=525).

Endometrium (n=525)	Frequency	Percentage
Benign		
Endometrial atrophy	114	21.71 %
Non-secretory endometrium	105	20.0 %
Endometrial polyp	97	18.48 %
Secretory endometrium	57	10.86 %
Proliferative endometrium	43	8.19 %
Endometrium with exogenous hormone effects	38	7.24 %
Autolyzed endometrium	17	3.24 %
Endometritis	13	2.48 %
Endometrial hyperplasia without atypia	5	0.95 %
Products of conception	2	0.38 %
Adenomyomatous polyp	1	0.19 %
Premalignant		
Endometrial hyperplasia with atypia	2	0.38 %
Endometrial polyp with atypia	1	0.19 %
Malignant		
Endometroid carcinoma	23	4.38 %
Serous carcinoma	4	0.76 %
Carcinosarcoma	1	0.19 %
Involved by Squamous cell carcinoma from the cervix	2	0.38 %
Total	**525**	**100.0 %**

The primary pathologies in the myometrium involved leiomyomata in 134 (25.52%) women, adenomyosis in 129 (24.57%) and both leiomyomata and adenomyosis in 87 (16.57%). Leiomyosarcoma was reported in 1/525 (0.19%) hysterectomies.

The most common pathology validated in the cervix was related to uterine prolapse in 104/520 (20.0%) patients, which displayed variable degrees of acanthosis and keratosis of the squamous mucosa, squamous metaplasia, ulceration and inflammation of the transitional zone. In 11 hysterectomies, representing 2.12%, endocervical polyps were identified. Cervical intraepithelial neoplasia (CIN) was reported in 2 (0.38%) cases and Squamous cell carcinoma in 6 (1.15%) cases. The pathological findings reported in the ovaries are supplemented in Table II. Fallopian tubes were received in 409 cases, salpingitis was reported in 10 (2.44%) and endometriosis in 4 (0.98%) patients. Primary serous carcinoma of the fallopian tubes was identified in 5 (1.22%).

There were 207 (39.42%) premenopausal women, 236 (44.95%) postmenopausal, and the menopausal status was not known for 82 (15.62%). These were further stratified into 5 years' age groups. The frequencies and percentages of women in the three menopausal categories in each 5-year age group is given in the figure 1.

Table II: Pathological findings in the ovaries (Oophorectomy in 400 cases).

Ovaries (n=400)	Frequency	Percentage
1. Benign conditions		
Normal histology or cystic follicles	322	80.50%
Endometriosis	10	2.50%
Tubo-ovarian abscess	3	0.75%
Stromal hyperplasia	3	0.75%
Ectopic gestation	2	0.5%
Ovarian torsion and infarction	1	0.25%
2. Benign cysts and tumors		
Serous cystadenoma	16	4.0%
Mucinous cystadenoma	8	2.0%
Mature cystic teratoma	8	2.0%
Brenner tumor	2	0.5%
Brenner and mucinous cystadenoma	2	0.5%
Fibroma	3	0.75%
3. Malignant tumors		
Serous carcinoma	10	2.50%
Granulosa cell tumor	7	1.75%
Endometrioid carcinoma	2	0.50%
Secondary involvement by SCC from the cervix	1	0.25%
Total	**400**	**100%**

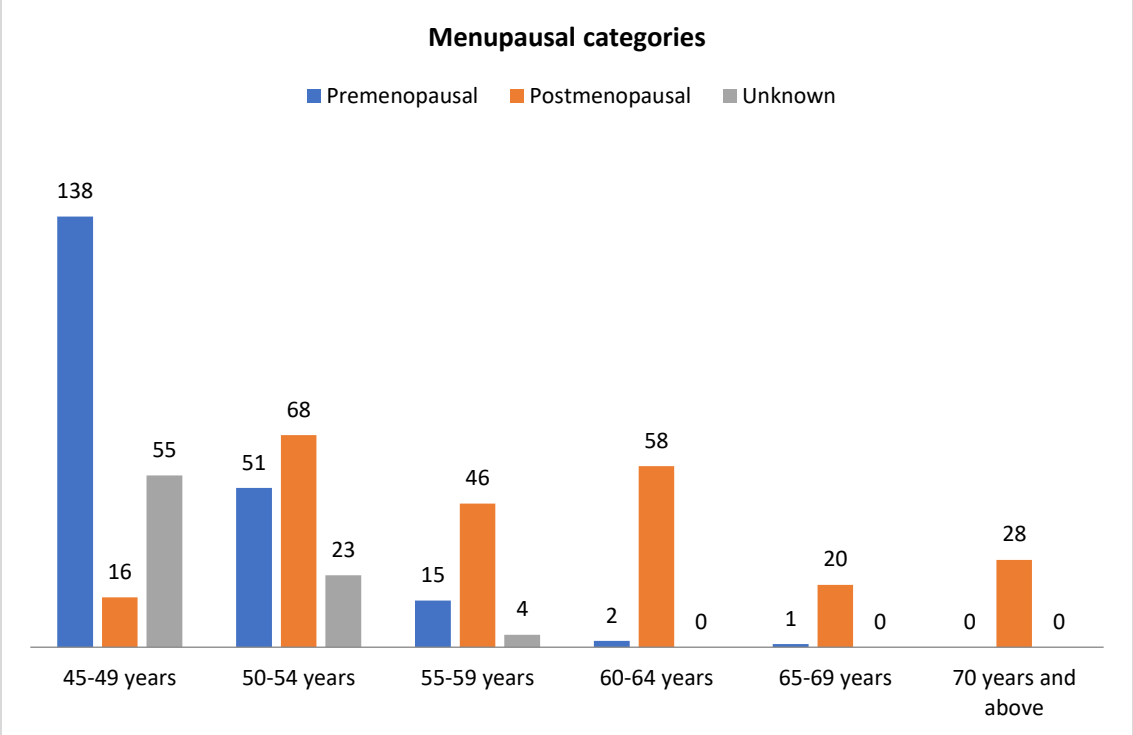

Figure 1: Menopausal categories of women according to their age groups.

Fisher exact and Chi square tests show significant differences in the frequencies of endometrial atrophy, adenomyosis and leiomyomata, uterine prolapse, endometrial cancer, ovarian cancer, and tubal cancer between the premenopausal and postmenopausal categories. Table III.

Table III: Correlation of the menopausal categories of the women with the pathological findings in the hysterectomy specimen.

Menopausal categories	Pathological findings in the hysterectomy specimens. N (% of women in each menopausal category)		Total	P value and test applied
	Endometrial atrophy	No endometrial atrophy	Total n (%)	
Postmenopausal	113 (25.51%)	123 (27.77%)	236 (53.27%)	P=0.00001 Fisher exact
Premenopausal	1 (0.23%)	206 (46.50%)	207 (46.72%)	
Total	114 (25.73%)	329 (74.27%)	443 (100%)	
Menopausal category	**Adenomyosis and/or Leiomyomata**	**No Adenomyosis or leiomyomata**	**Total n (%)**	**P value, test applied**
Postmenopausal	113 (25.51%)	123 (27.77%)	236 (53.27%)	P=0.00001 Chi square
Premenopausal	176 (39.73%)	31 (7.0%)	207 (46.73%)	
Total	289 (65.24%)	154 (34.76%)	443 (100%)	
Menopausal category	**Uterine prolapse present**	**No Uterine Prolapse**	**Total n (%)**	**P value, test applied**
Postmenopausal	89 (20.09%)	147 (33.18%)	236 (53.27%)	P=0.00001 Chi square
Premenopausal	10 (2.26%)	197 (44.47%)	207 (46.73%)	
Total	99 (22.34%)	344 (77.65)	443 (100%)	
Menopausal category	**Endometrial cancer**	**No endometrial cancer**	**Total n (%)**	**P value, test applied**
Postmenopausal	23 (5.19%)	213 (48.08%)	236 (53.27%)	P=0.0002 Fisher exact
Premenopausal	3 (0.68%)	204 (46.05%)	207 (46.73%)	
Total	26 (5.87%)	417 (94.13%)	443 (100%)	
Menopausal category	**Ovarian cancer**	**No ovarian cancer**	**Total n (%)**	**P value, test applied**
Postmenopausal	14 (4.28%)	126 (38.53%)	140 (42.81%)	P=0.0008 Fisher exact
Premenopausal	3 (0.92%)	184 (56.27%)	187 (57.19%)	
Total	17 (5.20%)	310 (94.80%)	327 (100%)	
Menopausal category	**Tubal cancer**	**No tubal cancer**	**Total**	**P value, test applied**
Postmenopausal	5 (1.50%)	140 (42.04%)	145 (43.54%)	P=0.015 Fisher exact
Premenopausal	0 (0%)	188 (56.46%)	188 (56.46%)	
Total	5 (1.50%)	328 (98.50%)	333 (100%)	

Discussion

In this study we have documented the principal benign and malignant histopathological findings in the uterus and adnexa, and presented a comparison between these findings in the premenopausal and postmenopausal women. The mean age of the women was 52 years and the most frequent clinical symptom leading to hysterectomy was AUB in 256 (48.76%), followed by uterine prolapse in 104 (19.81%). AUB has been the primary indication for hysterectomy in most studies from Pakistan and India.[7,8,9] According to an international study, hysterectomy rates are highest for women in the age bracket of 40-49 years, uterine prolapse is the most consistent indication in the women over 55 years, and leiomyoma in the younger women.[10] Endometrial atrophy was the most frequent pathological finding in the endometrium, which was in conformity with previously published rates of 29% in an Indian study and 24.3% in a Nepalese study.[11, 12] additionally; we have verified a strong association between endometrial atrophy and postmenopausal status in women. As estrogen is required for endometrial persistence, endometrial atrophy ensues after menopause, leading to collapsed endometrial surface, microerosions, and irregular bleeding.[13] In the current study, 97 patients (18.48%) had endometrial polyps, and 7 (1.33%) had endometrial hyperplasia. According to a study by Danish et al., endometrial polyps were the most prevalent organic cause of AUB (22%), followed by hyperplasia (14%), in the endometrial biopsies.[14] Patil et al. have reported a rate of 12% for hyperplasia without atypia and 2.7% for

hyperplasia with atypia.[9] An article from Yemen reported a very high frequency of endometrial hyperplasia of 58.3% in the hysterectomies performed there.[15] In the present study, primary endometrial cancer was diagnosed in 28 hysterectomies (5.33%), and it significantly correlated with the postmenopausal status in women. The rate of endometrial cancer was consistent with 5.46%, reported in a study from Pakistan.[7] Most studies—Patil et al., 1.3%; Zaid et al., 1.7%; and Bukhari et al., 2%—report a low frequency of endometrial cancer.[9, 15, 16] Endometrial cancer has been linked to advancing age, increasing basal metabolic rate, diabetes, hypertension, recurrent vaginal bleeding and increased endometrial thickness, by the studies assessing the clinical risk for the prediction of cancer in postmenopausal women.[17,18]

Leiomyomata are the most frequent benign tumors of the myometrium, while adenomyosis is the ectopic presence of endometrial glands and stroma within the myometrium.[19,20] Both the conditions are attributed to high estrogen levels and present during the reproductive years with AUB, infertility, pelvic pain and mass, but menopause induces a natural regression to symptoms.[19,20] Leiomyomata were diagnosed in 25.52% of our cases, adenomyosis in 24.57%. Both the conditions coexisted in 16.57% and their frequency was significantly higher in the premenopausal women. The rates for leiomyoma are 27.2% and 31.2 %, for adenomyosis 20.5 % and 27.4% and for both lesions 15.8% and 6.4% by Bukhari and Zaid et al respectively.[15, 16] We report leiomyosarcoma in only one patient (0.2%). A 2015 meta-analysis indicated that there were only 32 instances of leiomyosarcoma in the 30,193 patients (0.11%) who underwent hysterectomy and myomectomy.[21]

Uterine prolapse is the displacement of the uterus into the vaginal canal.[22] Multiparity, obesity, asthma, and chronic constipation are established risk factors, while other factors that contribute are progressive denervation, decreasing collagen in the pelvic floor, and declining estrogen levels.[22] Mild uterine prolapse affects at least 50% of all pregnant women and its incidence increases with age.[22] Uterine prolapse was the second prevalent clinical indication for hysterectomy in 104 (20%) women, which was confirmed microscopically and a positive correlation with the postmenopausal state was additionally observed. The rate of uterine prolapse is comparable to 18.25% in Nepal, but lower than the stated prevalence of 28% in India and higher than 5.2% in Yemen.[9,12,15] In the current research, carcinoma of the cervix was reported in 6 (1.15%) of the cases and CIN in 2 (0.38%). An Indian study found a higher rate of cervical cancer at 5.8% and CIN at 7.0%; Nepalese research found CIN and carcinoma of the cervix in 3.6% of the hysterectomy patients.[23, 24]

The frequency of primary ovarian cancer was 19/400 oophorectomies (4.75%), predominantly diagnosed in the postmenopausal women. Primary tubal cancer was detected in 5 (1.22%) patients, all in the postmenopausal women. Research in Pakistan found that 0.27% of women aged 50 to 70 had ovarian cancer.[7] According to a study from Nepal, ovarian cancer occurs with a frequency of 3%.[24] Ovaries had a normal histology in 322 (80.5%) cases. Parker et al. have established that oophorectomy has a negative impact on the health of women of all ages by causing a decline in cognitive health, increasing the risk of cardiovascular disease, hypertension, osteoporosis and bone fractures, depression and dementia, thus increasing overall mortality.[25] Literature has proved that ovaries continue to synthesize androgens after menopause, which are converted to estrogen in the peripheral tissues.[25] The distal tubal epithelium is now considered to be the origin of the majority of high-grade ovarian cancers.[26] The Royal College of Obstetricians and Gynaecologists (RCOG) now recommends bilateral salpingectomy to reduce the risk of ovarian cancer while preserving the ovaries after hysterectomy.[27] Given that the majority of the ovaries in this study displayed a normal histology and that ovarian cancer was uncommon, particularly in the premenopausal women, we would advise a full workup before considering hysterectomy surgery. Ovarian conservation should be considered in patients who have no adnexal pathology, no clinical or radiological indication of gynaecological cancer, and no family history of ovarian malignancy.

Our study showed that stratifying the patients into age groups, 7.7 % of women in the age bracket of 45-49 years were menopausal, the percentage increased to 47.9% in 50-54 years to about 100% at 60 years. Life expectancy for women in Pakistan was 69 years in 2020, compared to 43 years in 1960, it is expected to increase further in the next decades and average age at menopause now is 47.8 $\pm$ 4.7 years.[28, 29] A women may have 20 or more years in her postmenopausal state, thus, in future additional resources would be required to focus on the morbidities associated with the older age group.

The strengths of the study were that it was histopathology-based research, which is regarded as the gold standard for the diagnosis of diseases, and

that it had a large sample size that was divided into premenopausal and postmenopausal patient categories and statistical associations were tested. A few limitations were that the menopausal status provided by the clinician could not be confirmed from the patients, and the status was also unavailable for a fraction of cases, which were excluded from the analysis and this may have affected the results. The retrospective design and a brief time frame were also a few deficits of the study.

Conclusion

The most common clinical presentation leading to hysterectomy in the women was abnormal uterine bleeding. The common benign pathologies in the hysterectomy specimens were endometrial atrophy, and uterine prolapse in postmenopausal women and leiomyomata and adenomyosis in premenopausal. The most common malignancy was endometrial carcinoma, underscoring the importance of histopathology of these specimens.

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C. Interpretation/ Analysis and Discussion

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