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A study to determine association of ovarian morphology with endometrial morphology and postmenopausal bleeding conducted in a tertiary care hospital

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ABSTRACT

Background: Postmenopausal ovaries are chiefly composed of stroma and continue to have potential for hormonal synthesis. Ovarian stromal hyperplasia and endometrial hyperplasia/cancer are often identified concurrently, suggesting that ovarian morphology may represent a marker of cancer risk among older women.

Methods: An observational analytical cross-sectional study was conducted. Morphology of endometrium and ovary was studied in the specimens of total abdominal hysterectomy with unilateral/bilateral salpingo-oophorectomy in females with postmenopausal bleeding.

Results: Forty two specimens of total abdominal hysterectomy with bilateral hysterectomy were studied. Age of patients ranged from 45 to 80 years. Majority of patients were in the age group 45-55 years. Average duration of menopause was 6.2 years ranging from 1.5 years to 30 years. Most common endometrial pathology noted was proliferative endometrium (20, 47.6%) followed by primary endometrial malignancy and endometrial polyp (14.3%). Majority of the ovaries were unremarkable (35.8%). Most common change noted was stromal hyperplasia (31.4%).

Conclusions: The study did not find statistically significant association between stromal hyperplasia/large ovary and high risk endometrial pathology.

Keywords: Endometrium, Ovary, Hyperplasia, Stroma, Postmenopausal bleeding

INTRODUCTION

During the reproductive years the structure and activity of a functional endometrium of the corpus proper undergoes regular cyclic changes in response to the ovarian hormones, estrogen and progesterone and reflect the pattern of ovarian hormone secretion.¹ Most postmenopausal ovaries shrink to a size approximately one half their sizes during the reproductive period and have gyriform external appearance, while some have a smooth surface. The cut surface is usually firm and predominantly solid, but occasional cysts which are several millimetres in diameter may be visible inside the cortex. Small white scars are typically present within the

medulla which represents corpora albicantia. Thick-walled blood vessels may be seen within medulla and hilus.²

Postmenopausal ovaries consist largely of stroma, which includes hormone synthesizing cells. Larger ovaries were more likely to contain luteinized cells and hilar cells, overall suggesting a link between size and potential for hormone synthesis.³ Ovarian stromal hyperplasia and endometrial cancer are often identified concurrently, suggesting that ovarian morphology may represent a marker of cancer risk among older women.⁴ Elfayomy and El Tarhouny in their study to verify association of ovarian volume assessed by transvaginal ultrasound with histological findings and sex hormones levels in women

with postmenopausal bleeding and thickened endometrium concluded that enlarged ovaries in women with postmenopausal bleeding and thickened endometrium are associated with endometrial adenocarcinoma risk and represent a marker of the availability of the androgens for peripheral estrogen synthesis, whereas obesity affects the degree of conversion.⁵ Therefore, the primary objective of this study was to determine association of morphological changes in ovary with morphological changes in endometrium in females with postmenopausal bleeding.

METHODS

An observational analytical cross-sectional study was conducted in the department of pathology of LT medical college and general hospital, Mumbai, over a period of two years from June 2017 to June 2019. Morphology of endometrium and ovary was studied in the specimens of total abdominal hysterectomy with unilateral/bilateral salpingo-oophorectomy. Forty two specimens were included in the study.

Inclusion criteria

All specimens of total abdominal hysterectomy with unilateral/bilateral salpingo-oophorectomy of postmenopausal women with complaint of postmenopausal bleed were included in the study.

Exclusion criteria

All specimens of total abdominal hysterectomy with unilateral/bilateral salpingo-oophorectomy where presenting complaint was other than postmenopausal bleed and patient's with leiomyoma or adenomyosis, laproscopically resected specimens, specimens where resection of only fallopian tube/ovary/myomas are carried out without removal of uterus and endometrial/ovarian biopsy were excluded from the study.

Procedure

Clinical history was studied by referring to requisition form sent along with the specimen and also by referring to case records maintained in hospital wards. The case record form included complaints: postmenopausal bleeding, examination: per abdomen, per vaginum, per speculum examination.

Investigations

USG: the hysterectomy specimens received from obstetrics and gynaecology department, after washing to remove the excessive blood, were fixed in 10 % buffered formalin. They were assessed for gross features as follows: uterine and adnexal dimensions, endometrium polyp, endometrial mass and cysts or mass in ovary. Subsequently the tissues were dehydrated with ascending grades of alcohol, cleared in xylene and embedded in

paraffin. Thereafter, 3-5 microns thick paraffin sections were cut on a rotary microtome dewaxed and stained with Haematoxylin and Eosin. Special stains were performed wherever considered necessary. Sections were studied by the senior pathologist with expertise in female genital tract pathology and diagnosis was made as per the standard text books.⁶⁻⁹ Microscopic findings noted were: endometrial thickness to look for endometrial hyperplasia, endometrial phase, endometrial carcinoma, atrophic endometrium, stromal changes like hyperthecosis, hyperplasia in ovary. Ovarian stromal hyperplasia was defined as diffuse or nodular proliferation of plump ovarian cortical stromal cells encroaching on the medulla, atrophic changes in ovary and presence of primordial, primary and secondary follicles.

Statistical analysis

For statistical analysis, ratio, Chi square test, student's paired and unpaired t test was applied wherever necessary.

RESULTS

Total no of gynaecology specimen received were 5475 including biopsy and hysterectomy specimens. Amongst postmenopausal women, 101 specimens of hysterectomy with bi/unilateral salpingo-oophorectomy were received. Of 101 cases 42 cases (41.6%) had complaint of postmenopausal bleeding per vaginum (PV) whereas 2nd most common complaint was of abdominal pain without bleeding per vaginum (27, 26.7%). Other cases presented with abdominal mass (18, 17.8%), uterovaginal prolapse (13, 12.8%) and one was known case of Carcinoma cervix (1, 0.9%). Detailed study of morphology of endometrium and ovary was performed on 42 specimens of total abdominal hysterectomy with unilateral or bilateral salpingo-oophorectomy received from females with postmenopausal bleeding (PMB). As we had included both unilateral and bilateral salpingo-oophorectomy with hysterectomy specimen, we got 36 right sided ovaries and 31 left sided ovaries. Distribution of various endometrial pathology in females with postmenopausal bleeding (n=42) (Table 1). Majority of the females showed benign morphology (31, 73.8%) of which proliferative endometrium was more common (20, 47.6%). Primary malignancy of endometrium was second common pathology along with benign endometrial polyp (14.3%). Varying ovarian morphology in females with PMB (Table 2). Some of the ovaries showed two types of lesions. Majority (35.8%) of the ovaries did not deviate from the usual morphology of ovary described in postmenopausal females. Most common change noted was stromal hyperplasia (31.3%) (Figure 1). Age of patients ranged from 45 to 80 years. Average age of the study group was 55.8 years majority of the patients were in 45-55 years age group and predominantly showed benign proliferative endometrium and stromal hyperplasia.

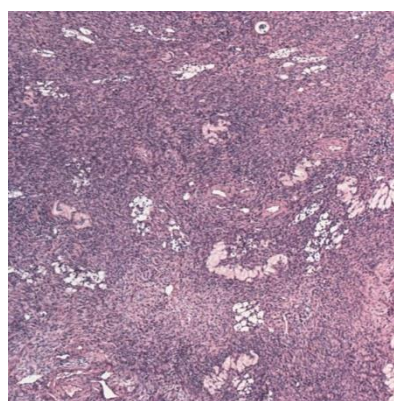


Figure 1: Ovarian stroma showing stromal hyperplasia in a female with postmenopausal bleed (H&E, 100X).

Table 1: Distribution of various endometrial morphology in females with PMB (n=42).

Type	Endometrial morphology	N	%
Benign	Atrophic endometrium	5	11.9
	Proliferative endometrium	20	47.6
	Endometrial polyp	6	14.3
Premalignant	Endometrial hyperplasia	4	9.5
Malignant	Endometrial carcinoma	6	14.3
	Metastasis	1	2.4
	Total	42	100

Premalignant endometrial hyperplasia and primary malignancy endometrial carcinoma & adult granulosa cell tumour ovary were seen in higher age group 56-65 years. Average duration of menopause was 6.2 years ranging from 1.5 years to 30 years. Significant morbidity causing morphological changes in endometrium and ovary occurred within 10 years of onset of menopause. However, endometrial carcinoma occurred after 10 years of menopause. Statistics showed a significant relationship of increasing duration of menopause and high risk endometrial pathology. No significant impact of parity was noted on various morphological changes in endometrium and ovary. Detailed study of association of stromal hyperplasia and large volume of ovary with morphology of endometrium was performed. In this study prevalence of stromal hyperplasia in ovary was observed to be 31.3% in females with PMB. In majority of the females stromal hyperplasia in ovary was associated with proliferative endometrium (42.9%) followed by endometrial carcinoma and atrophy (19% each) (Table 3).

Further we attempted to analyse that whether there is any exposure and outcome relationship between ovarian stromal hyperplasia and significant endometrial pathology that can cause PMB. For this purpose endometrial morphology of 'atrophy' was considered as absence of pathology in endometrium and endometrial morphology including proliferative endometrium, benign endometrial polyp, premalignant endometrial hyperplasia,

and endometrial carcinoma was considered as presence of endometrial pathology.

Table 2: Ovarian morphology in females with PMB (n=67).

Ovarian morphology	No. of cases right ovary (36)	No. of cases left ovary (31)	Total N (%)
Stromal hyperplasia	10	11	21 (31.3)
Follicular cyst	6	4	10 (14.9)
Corpus luteal cyst	1	2	3 (4.5)
Benign serous tumours	5	2	7 (9)
Mature cystic teratoma	1	0	1 (1.5)
Adult granulosa cell tumour	0	1	1 (1.5)
Fibrothecoma	1	0	1 (1.5)
Metastasis	1	1	2 (3.0)
Unremarkable	13	11	24 (35.8)
Total number of lesions	38	32	-

Table 3: Comparison of endometrial morphology with ovarian stromal hyperplasia (n=21).

Endometrial morphology	Percentage of stromal hyperplasia
Atrophy	4 (19)
Proliferative endometrium	9 (42.9)
Benign endometrial polyp	1 (4.8)
Endometrial hyperplasia	3 (14.3)
Endometrial carcinoma	4 (19)

Unremarkable ovaries were counted as ovaries with stromal hyperplasia absent. Ovaries with other pathology were not included in this calculation so as to prevent effect of confounding factors. Prevalence odds ratio of endometrial pathology was studied in relation to presence or absence of stromal hyperplasia as shown in (Table 4). Calculations were done as follows: P1 prevalence of endometrial pathology in cases with ovarian stromal hyperplasia= $a/a+b=17/21=0.81=81\%$. P0 prevalence of endometrial pathology in cases without ovarian stromal hyperplasia= $c/c+d=22/24=0.91=91\%$. Prevalence ratio= $a/a+b/c/c+d=81/91=0.89$. Prevalence odds ratio= $ad/bc=17 \times 2 / 22 \times 4 = 0.39$. In forty women with postmenopausal bleeding, relationship between endometrial thickness and ovarian volume was studied, to determine the impact of volume of ovary on presence/absence of premalignant or malignant pathology in endometrium and thus evaluate whether ovarian

volume can be a diagnostic parameter for premalignant/malignant pathology or can lead to bleeding PV. Of 40 patients 31 patients had benign endometrial lesions (group I) and 9 patients (group II) had premalignant and malignant endometrial pathology (Table 5).

Table 4: Prevalence ratio of stromal hyperplasia in females with PMB.

No. of ovaries with	Endometrial pathology present	Endometrial pathology absent	Total
Stromal hyperplasia present	17(a)	4(b)	21(N1)
Stromal hyperplasia absent	22(c)	2(d)	24(N0)
Total	39	6	45

Table 5: Endometrial pathology in 40 patients with postmenopausal bleeding selected to know the impact of ovarian volume.

Endometrial pathology			
Group I (benign)		Group II (malignant)	
Histopathology diagnosis	N	Histopathology diagnosis	N
Endometrial polyp	8	Endometrial carcinoma	7
Endometrial hyperplasia without atypia	1	Endometrial sarcoma	1
Atrophic endometrium	2	Metastatic malignancy	1
Proliferative endometrium	18		
Disordered proliferative endometrium	2		
Total	31	Total	9

Endometrial thickness considered here was from ultrasonography. Each ovary was measured in 3 dimensions and ovarian volume was calculated using the prolate ellipsoid formula ($L \times H \times W \times 0.523$).¹⁰ Statistical t-tests showed significant difference in the endometrial stripe thickness between the two groups at p value of 0.01645. However, p values of 0.195 and 0.669 from t-test confirmed that there was no significant difference in the means of ovarian volume between the group with benign endometrial lesions and the group with premalignant and malignant endometrial lesions (Table 6).

Relationship of ovarian volume with benign, premalignant and malignant pathology of endometrium

was evaluated taking the cut off volume of ovary as 5.8 ml and 3.5 ml to evaluate any impact of ovarian volume on development of benign or malignant lesions in endometrium.^{11,12}

Table 6: stripe thickness and ovarian volume of groups I and II.

Ovarian volume/Endometrial thickness	Group I (N=31) Mean ±SD	Group II (N=9) Mean ±SD	P value	Significance
ET (cm)	0.35± 0.29	1.45± 2.51	0.01645	Yes
Right ovarian volume (ml)	10.18± 34.47	2.04± 2.57	0.1958	No
Left ovarian volume (ml)	8.93± 25.82	15.83 ±42.09	0.6693	No

All 26 patients in Group I with benign morphology had ovarian volume measurements <5.8ml. In Group II, with premalignant and malignant conditions, 6 had ovarian volume measurements <5.8 ml while 3 had ovarian volume measurements more than 5.8 ml. Linear regression analysis showed no significant association between increased ovarian volume and the presence of premalignant and malignant endometrial conditions (p=0.4606). Based on this study, using the mean ovarian cut off of 5.8 ml for postmenopausal women, a value less than 5.8 ml reassured that 37.5 percent of the patients did not have malignant endometrial condition (NPV=37.5%) and had a specificity of 34% in correctly identifying those who did not have endometrial malignancy on initial screening. On the other hand, an ovarian volume greater than 5.8 ml had 83.87% sensitivity in picking up endometrial carcinoma. However, it had a positive predictive value of 81.25% in confirming a patient with endometrial malignancy (Table 7). As Asians have small ovarian volume, cut off of ovarian volume was lowered to 3.5ml.¹⁴ the ovarian volume as a screening parameter was also not significant in determining benign and malignant endometrial conditions at p value of 0.3882. Cut-off value of 3.5ml showed high sensitivity and low specificity of 80.64% and 33.4%, respectively, with a high positive predictive value of 80.64% and a negative predictive value of 33.4% (Table 8). Lowering the cut-off to 3.5ml did not improve the specificity and positive predictive value.

DISCUSSION

Post-menopausal bleeding is a serious complaint. More often than not, an organic cause is not identifiable and the histopathology may show atrophic endometrium,

proliferative endometrium and rarely secretory endometrium.

Table 7: Correlation of ovarian volume cut-off of 5.8 ml with benign and premalignant/malignant endometrial lesions.

Ovarian volume cut off	Group 1 (benign)	Group 2 (pre malignant/ malignant)
<5.8 ml	26	6
>5.8 ml	05	3
Total	31	9

Chi square value=0.009766, p value=0.4606, sensitivity 83.87%, specificity 34%, positive predictive value=81.25%, negative predictive value=37.5%, diagnostic accuracy=70%.

Table 8: Correlation of ovarian volume cut-off of 3.5ml with benign and premalignant/malignant endometrial lesions.

Ovarian volume cut off	Group 1 (benign)	Group 2 (pre malignant/ malignant)
<3.5 ml	25	6
>3.5 ml	6	3
Total	31	9

Chi square value=0.08065, p value=0.3882, sensitivity 80.64%, specificity 33.4%, positive predictive value=80.64%, negative predictive value=33.4%, diagnostic accuracy=67.5%.

These lesions are thought to be related to hyperestrinism in premenopausal and perimenopausal women.¹³⁻¹⁵ Morphological changes in aging ovary, considered as pathological, may also induce some hormonal changes. Ovarian hyperthecosis, a diffuse stromal hyperplasia with nests of luteinized cells, as well as stromal hyperplasia, may be associated with estrogenic or progestagenic effects. Stromal hyperplasia most commonly seen in postmenopausal patients may be associated with raised androgen levels and also with endometrial adenocarcinoma. Jongen et al studied the relationship between the presence of endometrioid cancer, degree of ovarian hyperplasia and ovarian steroid production in postmenopausal women. Results showed higher degree of ovarian stromal hyperplasia in the presence of endometrioid endometrial cancer. Likewise, increasing degree of ovarian stromal hyperplasia was related to higher ovarian levels of both testosterone and androstenedione ($p < 0.05$ and $p < 0.005$, respectively) but not to oestrone and estradiol.¹⁶ Postmenopausal estrogens originate from the peripheral conversion of androgens which are produced by the adrenal glands and the ovaries.¹⁷ In a very recent study, Fogle et al investigated whether the postmenopausal ovary is hormonally active and contributes to the circulating pool of androgens. They analyzed serum levels of testosterone, androstenedione, dehydroepiandrosterone, oestrone and estradiol preoperatively, intraoperatively and postoperatively among postmenopausal women undergoing total

abdominal hysterectomy with bilateral salpingo-oophorectomy. They concluded that postmenopausal ovary remains hormonally active, secreting significant amounts of androgens and estrogens and persists in women as long as 10 years beyond menopause. This phenomenon may be marked in menopausal women with increased ovarian volume.¹⁸ Initial studies demonstrated by Northern analysis showed that only ovaries from postmenopausal women with endometrial hyperplasia or cancer expressed all the enzymes necessary for androgen synthesis.¹⁹ In 1942 Smith Johnson and Hertig discussed ovarian stromal hyperplasia.²⁰ They noticed some changes in postmenopausal ovaries which seemed to be commonly associated with hyperplastic bleeding endometrium. The main characteristic of these changes was described as the presence of “masses of dense well vascularised, stromal tissue in either the cortex or the medulla of the ovary with a tendency to form whorls.”

In Ghosh et al study out of the 62 total cases having endometrial hyperplasia, 53 cases (83.5%) had one or more subtle ovarian stromal changes and 9 cases (14.5%) lacked the ovarian stromal changes.²¹ Out of the 50 cases without endometrial hyperplasia, only eight had subtle ovarian changes. In the 53 cases, which showed ovarian stromal changes, the changes were found in combination and variable proportions. Jones and Brewer found very little evidence of oestrogen stimulation in the uninvolved portions of endometrium and described no ovarian changes while studying the endometria and ovaries in 68 women with endometrial carcinoma.²² Mossman and Zheleznev et al in their studies also told that there was no significant association between interstitial glands and estrogen.^{23,24} This study was not restricted to endometrial hyperplasia or endometrial malignancy. In the present study population of 42 females with PMB, ovary stromal hyperplasia was noted in 15 females (35.7%) and in 21/67 ovaries (31.4%) studied. Prevalence ratio and prevalence odds ratio did not show significant association between presences of stromal hyperplasia in ovary and pathologically significant morphology in endometrium. Though, premalignant and malignant lesions of endometrium were seen only in 10/42 cases, but 7 showed stromal hyperplasia in ovary. This number is but small and observations cannot be generalised on a larger population.

Recent data suggest that postmenopausal women with larger ovaries are at increased risk for endometrial carcinoma; hence ovarian volume measurements in association with endometrial pathology have been investigated. Several investigators have set different cut-off measurements of ovarian volume for menopause. Aboulgar, et al. determined the postmenopausal ovarian volume to be $3.4 \pm 1.7 \text{ cm}^3$. Goswamy calculated it at $3.58 \pm 1.40 \text{ cm}^3$. Aviram et al stated an ovarian volume of $3.4 \pm 2.2 \text{ cm}^3$. Callen set it at $5.8 \pm 3.6 \text{ cm}^3$.²⁵ this was the cut-off value used in this study. Sherman et al investigated the

association of ovarian volume with cancer among postmenopausal women. In his study, postmenopausal women aged 55 to 59 without cancer had a mean ovarian volume of 1.25 cm³ which declined further to 1.0cm³ between 65 and 69 years. However, those with endometrial cancer had bigger volume with mean ovarian volume greater or equal to 3.0cm³. They concluded that large ovaries among postmenopausal women may represent a marker of risk for hormonally related tumour like endometrial cancer.²⁶ The enlarged ovarian volume among postmenopausal women could be explained by stromal hyperplasia.

The primary objective of this study was to determine the ovarian volume in women with postmenopausal bleeding and to investigate its association with endometrial malignancy. Results showed that smaller ovarian volumes were associated with benign endometrial conditions and bigger ovarian volumes were seen in those with premalignant and malignant conditions. 31 patients in group I with benign histopathologic diagnosis and ovarian volume of less than 5.8 ml which showed a negative predictive value of only 37.5% and a specificity of only 34% in finding a normal or benign endometrial condition among those negative for malignancy. 6 patients from group I showed ovarian volume more than >5.8 ml as we had benign serous cyst adenomas with higher volume of 1350 ml. Higher as well as smaller ovarian volumes were seen in those with premalignant and malignant conditions. Of the 9 patients in group II, 3 had ovarian volume >5.8 ml and 6 had ovarian volume <5.8 ml. The cut-off value of 5.8 ml had 83.87% sensitivity of picking up or identifying malignant endometrial condition and had a positive predictive value of 81.25% in confirming a patient with endometrial malignancy. The cut-off was highly sensitive in picking up malignant endometrial conditions and can truly identify those with benign endometrial conditions, it yielded low specificity value. This could probably be explained by the cut off ovarian volume used at 5.8 ml, too high for Asians. The smaller ovaries among Asians were also consistent with their data showing that Asians have lower testosterone levels hence, if cut-off value was lowered to 3.5ml, the ovarian.²⁷ Volume as a screening parameter was also not significant in determining benign and malignant endometrial conditions at p value of 0.3882. Cut-off value of 3.5ml showed high sensitivity and low specificity of 80.64% and 33.4%, respectively, with a high positive predictive value of 80.64% and a negative predictive value of 33.4%. Lowering the cut-off to 3.5 ml did not improve the specificity and positive predictive value and the results showed considerable overlap in the endometrial thickness between patients with benign and those with malignant conditions. There was significant difference in the endometrial stripe thickness between the two groups. However, in the presence of a thickened endometrium, coupled with an increased ovarian volume, the probability of having a malignant condition is increased.

Limitations

Limitations of current study were; serum sex steroid levels were not analysed and no record of obesity and BMI was included (important risk factors for PMB).

CONCLUSION

The study thus did not find any statistically significant association between ovarian morphology and endometrial pathology. However, it suggests that probability of endometrial malignancy is increased with larger ovarian volume and stromal hyperplasia. This study was a limited period study in a tertiary care hospital. Larger population based studies covering moderate to high risk patients of different strata, may reveal different results and may help in devising early screening test protocols for preventing development of high risk endometrial pathology in postmenopausal females.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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