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A critical appraisal of the spectrum of polypoidal lesions of uterus: A pathologists' perspective

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Abstract: *Background:* Polypoidal lesions of the uterus are clinically significant as they may either clinically mimic or harbour endometrial hyperplasia or malignancy. *Material & Methods:* A retrospective analysis was conducted over a three period (2012-2015) for all the polypoidal lesions of the uterus. All the clinical details of the patients, that is, age, menopausal status, obstetric history, signs and symptoms, co-morbidities like diabetes mellitus (DM) and hypertension, size of the polyp, its location in uterus and final histopathological diagnosis were recorded and analysed. Immunohistochemistry was performed wherever required. Pathological spectrum of polypoidal lesions, the incidence of premalignancy and malignancy as well as correlation with other clinicopathological parameters was evaluated. *Results:* Out of a total of 44 polypoidal lesions, 37(84.09%) were benign, 11.36% were hyperplastic/ premalignant while only 2 polypoidal lesions (4.54%) were malignant. Out of 37 patients with benign polyps (group 1), 4 were diabetic while 4 out of 7 patients with premalignant and malignant polyps (group 2) were diabetic, the difference being statistically significant. There were no significant differences in age, polyp size, parity, menopausal status and hypertension between the two groups. *Conclusions:* Although the sample size of the study was small, based on our observations, we wish to reemphasize the importance of careful histopathological scrutiny of all uterine polypoidal lesions to rule out any premalignant or malignant focus. Moreover, diabetics with uterine polyps should be cautiously handled as DM was significantly associated with incidence of premalignant/ malignant lesion.

Keywords: Polyps, endometrial, polypoidal lesions, uterus, malignancy, hyperplasia.

Introduction

Endometrial polyps are tissue outgrowths which are generally benign, may be attached to the uterus by a pedicle (pedunculated or may have a base (sessile). These patients usually develop abnormal uterine bleeding (AUB) [1]. Rarely, myometrial lesions like fibroid or adenomyoma can give rise to polypoidal growths into the endometrial cavity. Endometrial polyps (EP) assume clinical significance as they may mimic endometrial hyperplasia due to increased endometrial thickness on ultrasound or endometrial cancers in postmenopausal women.

Moreover, occasionally endometrial polyp may harbour endometrial hyperplasia or even malignancy. Therefore, it becomes increasingly important for EP to be carefully scrutinized histopathologically to rule out any premalignant or malignant focus. Several authors have evaluated the incidence of malignancy in endometrial polyps [2-4]. Many researchers have also analysed the association between various risk factors like postmenopausal status, hypertension, obesity, diabetes mellitus etc in the development of malignant transformation in patients with endometrial polyps with variable results [5-7]. We conducted this study to analyse the pathological spectrum of polypoidal lesions of uterus, the incidence of premalignant and malignant change as well as to evaluate the correlation between hypertension, diabetes mellitus, parity and postmenopausal status with malignant transformation in polypoidal lesions of uterus.

Material and Methods

We conducted a retrospective analysis of all cases which presented with polypoidal lesions

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of uterus either clinically or as an incidental finding, over a period of three years (april 2012-april 2015). The specimens included in the study were endometrial biopsies, polypectomies and hysterectomies. The study included women from all age groups including postmenopausal females. Postmenopausal female was the one with atleast 12 months amenorrhea after the age of 45 years. Abnormal uterine bleeding (AUB) was defined as any vaginal bleeding in postmenopausal women (not on hormone replacement therapy, HRT) or irregular vaginal bleeding in reproductive age female.

The requisition forms, pathology reports and slides of all the cases were retrieved from the archives of department of Pathology, Hamdard institute of Medical Sciences and Research, New Delhi. Immunohistochemistry was performed wherever required for confirmation of the diagnosis. All the clinical details of the patients, that is, age, menopausal status, obstetrics history, signs and symptoms, co-morbidities like diabetes mellitus and hypertension, size of the polyp, its location in uterus and final histopathological diagnosis were recorded and analysed.

Statistical analysis: All Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 17 software for windows (SPSS, INC, Chicago, IL). Chi-square test was used to compare categorical/dichotomous variables. P value of ≤ 0.05 was considered significant.

Results

A total of 44 polypoidal lesions of uterus were encountered over a period of 3 years. Most of the polypoidal lesions occurred in women in the age group 31-50 years (54%). None of the patients were less than 20 years of age. 56.82% (25/44) were premenopausal while 43.18% (19/44) were postmenopausal. An analysis of the clinical presentation of these patients revealed that most common presenting feature was abnormal uterine bleeding (AUB) (20/44; 45.45%), followed by fibroid uterus on sonography (15/44; 34.09%) and postmenopausal bleeding (10/44; 22.13%). Few patients had more than 1 presenting complaint. One 65 year old female was a known case of metastatic carcinoma ovary stage IIIC, who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy following chemotherapy. Endometrial polyp was discovered incidentally in this patient. Four patients presented with primary or secondary infertility and polyp was discovered either on sonography or diagnostic hysteroscopy.

Most of the polyps were 2-4 cm in maximum dimensions (26/44; 59%) while only a few were < 1cm (2/44) or >4 cm (4/44) in size. The two malignant polyps encountered in the study were 9 and 7.5 cm each. In terms of parity, most of the females were para 1 to 4 (30/44; 68%). Fundus of the uterus was the commonest location for polyps (17/44;38.64%) followed by body (13/44;29.54%) and both fundus and body (10/44; 22.73%). Clinicopathological profile of all the polypoidal lesions of uterus is depicted in table I.

Fig-1: Photomicrograph from atrophic polyp showing cystically dilated glands lined by atrophic epithelium (Hematoxylin and Eosin, 400X)

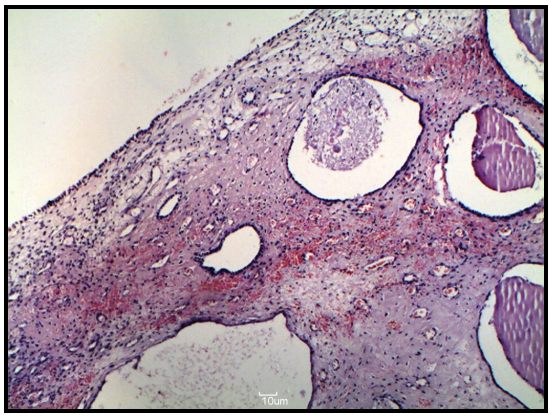
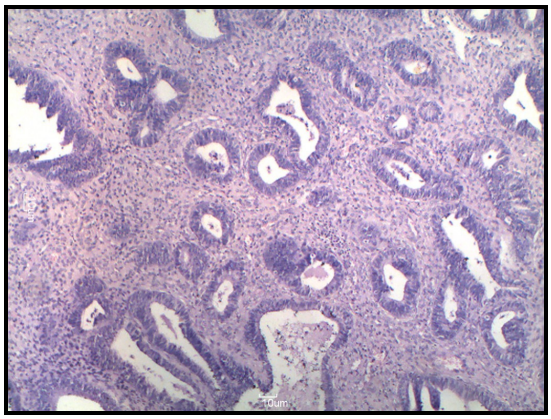


Fig-2: Photomicrograph from polyp with simple hyperplasia without atypia showing increased gland to stroma ratio, endometrial glands lined by tall columnar lining with pseudostratification at places (Hematoxylin and Eosin, 400X)



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On histopathological evaluation, most of the polyps turned out to be benign (37/44; 84.09%) (figure 1), 11.36% were hyperplastic/ premalignant while only 2 polypoidal lesions (4.54%) turned out to be malignant. The pathological spectrum of all polypoidal lesions is shown in table II. Most common diagnosis was functional endometrial polyp. Among the hyperplastic polyps, 4 were simple hyperplasia without atypia (figure 2) and one was complex hyperplasia with atypia.

Table-1: Clinicopathological Profile of all polypoidal lesions of Uterus (n=44)

Sl. No.	Feature	Categories	Number of Cases	Percentage (%)
1.	Age	< 20 years	0	0
		21-30 years	5	11.36
		31-40 years	14	31.82
		41-50 years	10	22.73
		51-60 years	7	15.91
		> 60 years	8	18.18
2.	Menopausal Status	Premenopausal	25	56.82
		Postmenopausal	19	43.18
3.	Clinical Presentation	AUB	20	45.45
		Fibroid	15	34.09
		Postmenopausal Bleeding	10	22.13
		Menorrhagia	7	15.91
		Infertility	4	9.09
		Ovarian tumor	3	6.82
4.	Size of Polyp (maximum dimension)	< 1 cm	2	4.54
		1-2cm	12	27.27
		2-3cm	16	36.36
		3-4cm	10	22.73
		>4cm	4	9.09
5.	Parity	Infertility	4	9.09
		1-2	10	22.73
		3-4	20	45.45
		5-6	7	15.91
		>6	3	6.82
6.	Location	Fundus	17	38.64
		Body	13	29.54
		Body & Fundus	10	22.73
		Isthmus	4	9.09

Table-2: Pathological Spectrum of all Polypoidal lesions of Uterus

Sl. No.	Category	Subcategory	Number of cases	Percentage (%)
1.	Benign		37	84.09
		Functional polyp	28	63.64
		Atrophic	4	9.09
		Leiomyomatous polyp	2	4.54
		Functional polyp with hormonal changes	2	4.54
		Adenomyomatous polyp	1	2.27
2.	Hyperplastic/ Premalignant		5	11.36
		Simple hyperplasia without atypia	4	9.09
		Complex hyperplasia with atypia	1	2.27
3.	Malignant		2	4.54
		Low grade endometrial stromal sarcoma	1	2.27
		Undifferentiated ESS	1	2.27

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We encountered 2 malignant polyps, both of which were sarcomatous. The first case, a 45 year old female first underwent polypectomy which turned out to be endometrial stromal sarcoma (ESS). Thereafter, total abdominal hysterectomy was performed and subsequent histopathology and immunohistochemistry (CD 10 and inhibin +) confirmed a diagnosis of low grade ESS. The second case, a 60 year old female had a large polypoidal lesion protruding into endometrial cavity which was clinically suspected to be a sarcoma. Microscopy revealed a highly pleomorphic sarcoma (figure 3) which was vimentin and CD10 + while cytokeratin, hormone receptors and smooth muscle actin (SMA) negative. Thus, finally it was labelled as undifferentiated ESS. We did not come across any endometrial adenocarcinoma presenting as a polyp.

Out of 37 patients with benign polyps, 4 were diabetic while 4 out of 7 patients with premalignant and malignant polyps were diabetic, the difference being statistically significant. There were no significant differences in age, polyp size, parity, menopausal status and hypertension between group 1 (benign polyps) and group 2 (premalignant and malignant polyps). The details are shown in table III.

Fig-3: Photomicrograph from a case of sarcomatous polyp showing oval to spindled cells with moderate to marked pleomorphism with increased mitoses (Hematoxylin and Eosin, 400X)

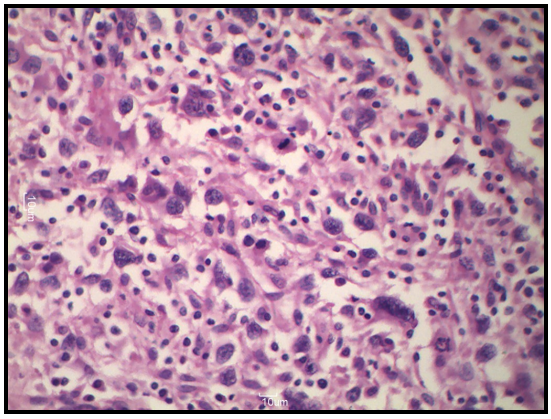

Table-3: Comparison between Group 1(benign polyps) and Group 2 (premalignant and malignant polyps)

	Group 1 (benign) (n=37)	Group 2 (premalignant &malignant) (n=7)	P value
Age (years) Mean (SD)	41 (1.25)	48 (1.43)	p=1.8
Polyp Size (cms) Mean (SD)	2.38 (0.90)	5.07 (2.82)	p= 0.73
Parity Mean (SD)	2.7 (1.58)	5.57 (1.27)	p=0.07
Menopausal Status Postmenopausal Premenopausal	 16 21	 3 4	p=0.86
Diabetes Mellitus Positive Negative	 4 33	 4 3	**p=0.014**
Hypertension Positive Negative	 3 34	 2 5	p=0.65

Discussion

Endometrial polyps are localized tissue outgrowths, either sessile or pedunculated, composed of a variable admixture of endometrial glands, stroma and blood vessels. They may undergo surface ulceration, bleeding or twisting. They are usually soft, but their consistency depends on the type [1]. Leiomyomatous polyps tend to be firm, grey white and show whorling while an adenocarcinomatous polyp tends to be soft,

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friable and maybe necrotic. Endometrial polyps are common in women of all age groups. There has been an increase in the incidence of polyps on account of wide usage of transvaginal sonography and sonohysterography. However, the incidence of malignancy in polyps is still low according to various studies in the literature [2-4].

In the general population, the prevalence of endometrial polyps may range from 6 to 38%. The polyps are most frequently found in women in the age group 40-50 years, thereafter their incidence starts waning. They are usually not seen before menarche [8]. This is in accordance with our study as we observed 54% of all the polypoidal lesions in 31-50 years age group. Endometrial polyps may arise anywhere in the endometrial cavity, although they are most frequently encountered in the fundus of uterus (near cornua) [9]. In the present study as well, most commonly polyps were found in fundus and body and fundus put together.

On rare occasions, myometrial lesions like fibroid or adenomyoma can give rise to polypoidal growths into the endometrial cavity. Submucosal fibroids are thought to originate from the inner myometrium, it is likely that in some cases relatively large fibroids arising from outer myometrium cause distortion of the cavity [10]. Adenomyoma of the uterus is a circumscribed nodular aggregate of benign endometrial glands surrounded by endometrial stroma with leiomyomatous smooth muscle. Adenomyoma may be located within the myometrium, or it may involve or originate in the endometrium and rarely grow as a polyp. Adenomyomatous polyps have the same appearance on gross examination as an ordinary endometrial polyp. Tahlan et al analysed 26 cases of uterine adenomyomas over a ten year period. Out of these, 4 presented with polyps for which polypectomy was performed [11].

The pathogenesis of endometrial polyps mainly rests on estrogen stimulation. Moreover, in susceptible patients, unopposed estrogen stimulation may predispose to the development of hyperplasia, atypia and even malignancy. A strong association exists between endometrial polyps and tamoxifen use. An association has also been suggested between endometriosis and presence of polyps in endometrium [1, 12].

Mihm et al in their series of 114 women (25-69 years age) reported presence of endometrial polyps in 35% females with AUB [13]. Relationship between polyps and infertility has also been evaluated by several authors. Shokeir et al found an incidence of 15.6% of endometrial polyps detected hysteroscopically in eumenorrheic infertile females [14]. Taylor et al reported that 29 % of women with primary infertility and 41% with secondary infertility had filling defects (polyps, fibroids, adhesions, septa) when dextran 70 was used vs. only 6-11% when CO_2 was used [15]. Malignancy developing in a polyp is very rare. We came across only 2 malignancies out of 44 polypoidal lesions, both of which turned out to be endometrial stromal sarcoma.

Although the occurrence of premalignant lesions and malignancy in endometrial polyps is low, many authors have studied various clinicopathological parameters which may be associated with such polyps like age, menopausal status, hypertension, obesity, diabetes mellitus (DM), hormone therapy, tamoxifen usage, size of polyp and AUB. Lenci et al found the incidence of premalignant lesions and cancer in endometrial polyps to be 2% (21/1020) and 0.5% (5/1020) respectively [2]. Topcu et al evaluated the risk factors for endometrial hyperplasia (EH) in endometrial polyps [5].

13 out of 203 patients showed EH. There were statistically significant differences in terms of age, menopausal status, morbid obesity and DM ($p<0.005$). Logistic regression demonstrated that menopausal status and DM were independent risk factors. Hypertension (HT) was also shown to be a risk factor related to malignant change in endometrial polyps by Savelli et al [6]. On the contrary, Cengiz et al did not find any clinical variables (DM, HT, HRT) to correlate with histopathology results in premalignant and malignant polyps [7]. In the present study, we came across 5 premalignant polyps including 4 cases of simple hyperplasia without atypia and a case of complex hyperplasia with atypia. However, we found significant differences between benign and premalignant and malignant polyps in relation to diabetes,

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but not with age, polyp size, parity, menopausal status and hypertension. We encountered only 2 malignant polyps which had a large size compared to benign polyps, however the difference was not statistically significant. Since the sample size of our study was small, we could not derive conclusions as to the factors which were significantly common in premalignant or malignant polyps.

Hileeto et al studied age dependent association of endometrial polyps with increased risk of cancer [3]. They found 66/513 malignant endometrial polyps during a ten year period, out of which the most common malignancy was endometroid adenocarcinoma. The frequency of malignant endometrial polyps increased with age and reached statistical significance in the age group >65 years ($p<0.001$). Malignancy rate in endometrial polyps ranges from 0-4.8% in various studies in the literature [4, 8, 16-18]. The reason for such variability could be bias due to small sample size of published studies and different geographical distribution of cancers. Another explanation could be a different proportion of high risk patients (increasing age, race, menopausal, obesity, HT, DM, on tamoxifen etc.) included in the study group. We found a malignancy rate of 4.54% (2/54) in the present study. Baiocchi et al found premalignant and malignant lesions confined to polyps to be 1.3 and 3.5% respectively [4]. Univariate analysis identified older age, menopausal status, presence of AUB and HT as significant factors associated with premalignant or malignant change in polyps.

Goldstein et al found that 31.1% (19/61) polyps in their study were diagnosed incidentally [16] while Cengiz et al found it to be 10.8% [7] similar to our study where 10% polyps were diagnosed on specimens sent to histopathology for reasons other than polyps. Lasmar et al assessed the correlation between polyp size and histopathological diagnosis of hyperplasia or cancer in 1136 patients [19]. They concluded that polyp size showed statistical significance among the variables analysed ($p<0.05$). Endometrial polyps >15mm showed a hyperplasia rate of 14.8% compared to 7.7% in the group with smaller polyps ($p<0.05$).

Conclusions

The most important limitation of the present study was the small number of endometrial polyps observed. Moreover, due to the retrospective nature of the study, the extraction of medical records becomes a challenge as all data is not available in all the cases.

Although the sample size of the study was small, based on our observations, we wish to reemphasize the importance of careful histopathological scrutiny of all uterine polypoidal lesions to rule out any premalignant or malignant focus. Moreover, diabetics with uterine polyps should be cautiously handled as DM was significantly associated with incidence of premalignant/ malignant lesion.

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