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HISTOPATHOLOGICAL STUDY OF ENDOMETRIUM IN WOMEN WITH ABNORMAL UTERINE BLEEDING

Pathology

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ABSTRACT

BACKGROUND – Abnormal uterine bleeding (AUB) is defined as a bleeding pattern that differs in frequency, duration and amount from a pattern observed during a normal menstrual cycle. The term dysfunctional uterine bleeding (DUB) is used to describe abnormal uterine bleeding for which no specific cause has been found. AUB is one of the most common gynaecological problems. This study was done to evaluate histological patterns of endometrium in women with abnormal uterine bleeding.

AIMS AND OBJECTIVE – To study various histological patterns of endometrium in abnormal uterine bleeding and correlate it with age, parity and symptoms.

MATERIAL AND METHODS – This is a retrospective study, conducted in the Department of Pathology, in a tertiary care hospital from 1st July 2016 to 30th June 2019. Total 718 specimens with AUB were included in the study from the age group of 21 to 95 years. The specimens received were hysterectomy (74.65 %), endometrial biopsies (21.45%), dilatation and curettage (2.79 %) and transcervical resection of endometrium (1.11 %).

RESULTS – The patients with AUB were mainly from the age group 41-50 years with menorrhagia as the chief complaint. Most of the women with AUB were multiparous (84.54%). The most common pattern observed on histopathological examination was proliferative endometrium (49.86%) followed by atrophic endometrium (10.31%). Malignancy was found in 2.23% (Endometrioid carcinoma – 1.81%, serous carcinoma - 0.14% and mucinous carcinoma – 0.28%). Endometrial hyperplasia without atypia (23 cases, 3.20%) was more common than endometrial atypical hyperplasia (EAH) / endometrioid intraepithelial neoplasia {EIN} (4 cases, 0.56 %). Various other patterns of endometrium on histopathology were endometritis (6.82 %) followed by endometrial polyp (4.46 %).

CONCLUSION – Histopathological examination of endometrium should be done generously in women presenting with abnormal uterine bleeding especially after the age of 40 years to rule out malignant pathology.

KEYWORDS

Abnormal uterine bleeding, endometrium, menorrhagia, histopathology

INTRODUCTION :

Abnormal uterine bleeding (AUB) is defined as uterine bleeding that is abnormal in duration, volume, frequency and/or regularity and has been present for the majority of the previous six months. [1] AUB that occurs without any systemic causes or any organic lesions of genital tract is referred as Dysfunctional Uterine Bleeding (DUB).[2] AUB is a common reason for women of all ages to consult their gynaecologist.[3] Histological patterns and causes of AUB show wide variation and range from normal endometrium to malignancy. It could be a sign of hormonal imbalance or a serious underlying condition necessitating aggressive treatment including a major surgical procedure. [3]

This study was carried out to evaluate the patterns of endometrial histological findings in women with AUB and to correlate these findings with age, parity and clinical features.

MATERIAL AND METHODS :

This is an observational retrospective study, proposed to study the endometrium in endometrial biopsies, dilatation and curettage specimens (D&C), transcervical resection of endometrium specimens (TCRE) and hysterectomy specimens received in the department of Pathology at tertiary care centre over the period of three years. This study included 718 cases of clinically diagnosed AUB.

All the specimens were fixed in 10% formalin. Detailed clinical history that included the age, chief complaints, menstrual history and obstetric history was retrieved from requisition form. After detailed gross examination, paraffin blocks of tissue were made; sections were cut and stained with hematoxylin and eosin. Microscopic examination of slides was done and findings were correlated with clinical and other relevant information.

RESULTS :

Out of the total 718 specimens received for abnormal uterine bleeding, 536 were hysterectomy specimen followed by endometrial biopsy (154 specimens), D & C (20 specimens) and TCRE (8 specimens).

The most common bleeding pattern in patients with AUB was menorrhagia (50.56%) followed by post menopausal bleeding (17.69%) and continuous per vaginal bleeding(15.60%) (Table 1). The age of the patient ranged from 21-95 years. Maximum numbers of patients were in the age group of 41-50 years. The mean age was 43.23 year.

Table 1 – Distribution Of Cases According To Clinical Presentation

Clinical presentation	No of cases	Percentage (%)
Menorrhagia	363	50.56
Post menopausal bleeding	127	17.69
Continuous per bleeding	112	15.60
Metrorrhagia	57	7.94
Dysmenorrhea	23	3.20
Menometrorrhagia	20	2.79
Abdominal pain	16	2.23
Total	**718**	**100.00**

Most of the patients of AUB were multiparous i.e. 607 cases (84.54%). The commonest endometrial pattern observed in patients with AUB was proliferative endometrium (358 cases, 49.86%) followed by atrophic endometrium (74 cases, 10.31%) and Secretory phase endometrium (69 cases. 9.61%). Correlation of endometrial histopathological findings with age is shown in table 2.

Table 2 – Distribution of cases and histopathological patterns according to age

Histopathological findings \ Age group (in years)		21-30	31-40	41-50	51-60	61-70	71-80	91-100	Total	Percentag(%)
Functional	Proliferative type endometrium	26	159	152	17	4	-	-	358	49.86
	Atrophic endometrium	-	-	32	20	16	5	1	74	10.31
	Secretory phase endometrium	9	31	27	2	-	-	-	69	9.61
	Disordered proliferative type endometrium	2	9	17	2	2	-	-	32	4.46
	Mixed pattern endometrium s/o hormonal imbalance	5	12	6	2	1	-	-	26	3.62
	Basal endometrium	3	4	2	2	-	-	-	11	1.53
Organic	Endometritis	6	26	13	3	-	1	-	49	6.82
	Endometrial polyp	2	11	12	5	3	2	-	35	4.87
	Endometrial hyperplasia without atypia	2	7	10	2	1	1	-	23	3.20
	Endometrial atypical hyperplasia/EIN	-	1	3	-	-	-	-	4	0.56
	Endometrioid carcinoma	-	2	3	7	1	-	-	13	1.81
	Serous carcinoma	-	-	-	-	-	1	-	1	0.14
	Mucinous carcinoma	-	-	-	2	-	-	-	2	0.28
Other	Inadequate	-	3	6	7	4	1	-	21	2.92
	Total	55	265	283	71	32	11	1	718	100

Amongst the cases with organic causes, the most common finding was endometritis comprising 49 cases (33.11 %), followed by endometrial polyp in 35 patients (23.65%) and endometrial hyperplasia without atypia (23 cases, 15.54%). Malignancy comprising of endometrioid carcinoma was seen in 13 cases (8.78%) followed by mucinous adenocarcinoma comprising of 2 cases (1.35 %). There was single case of serous carcinoma (0.68%) found in the age group of 71-80 years. The most common age group for endometrioid carcinoma was 51- 60 years whereas endometrial hyperplasia was seen in patients decade earlier.

Table 3 - Correlation of Endometrial histological findings with clinical presentation

Histopathological findings \ Clinical presentation		Abdominal pain	Continuous per bleeding	Dysmenorrhea	Menometrorrhagia	Menorrhgia	Metrorrhagia	Post menopausal bleeding	Total	Percentag(%)
Functional	Proliferative type endometrium	11	44	8	16	184	41	54	358	49.86
	atrophic endometrium	2	25		1	19	1	26	74	10.31
	Secretory phase endometrium	1	5	2		44	7	10	69	9.61
	Disordered proliferative type endometrium		5	1	1	18		7	32	4.46
	Mixed pattern endometrium s/o hormonal imbalance		3			20	1	2	26	3.62
	Basal endometrium		5			5	1		11	1.53
Organic	Endometritis	1	3	10	2	27	1	5	49	6.82
	Endometrial polyp		16	1		11		7	35	4.87
	Endometrial hyperplasia without atypia		3			14	1	5	23	3.20
	Endometrial atypical hyperplasia					2	1	1	4	0.56
	Endometrioid carcinoma	1	1			5	1	5	13	1.81
	Serous carcinoma					1			1	0.14
	Mucinous carcinoma							2	2	0.28
Other	Inadequate		2	1		13	2	3	21	2.92
	Total	16	112	23	20	363	57	127	718	100

Out of 49 cases of endometritis, 27 cases had menorrhagia as the most common clinical presentation. Most of these cases were in the age group of 31-40 years. Most of the cases of endometrial polyp and endometrial hyperplasia without atypia and atypical endometrial hyperplasia were found in the age group of 41-50 years with mean age of 47.11 years, 44.08 years and 43.25 years respectively. Most of the cases of endometrial polyp presented with continuous per vaginal bleeding (16/35cases), endometrial hyperplasia without atypia presented with menorrhagia (14/23 cases) and atypical endometrial hyperplasia presented with menorrhagia (2 cases).

Out of 16 cases of malignancies endometrioid carcinoma, mucinous carcinoma and serous carcinoma) were found. 31.25 % cases in the premenopausal group whereas 68.75 % were seen in the postmenopausal group which is approximately two times higher than premenopausal age group.

DISCUSSION :

Abnormal uterine bleeding occurs in reproductive women of all ages but is more common in adolescent and perimenopausal women.[4]

The maximum number of cases of AUB in our study was in the age group of 41-50 years (283, 39.42%). It is comparable to the other studies Sawke et al, Mishra et al and Prathipaa et al as shown in Table 4

Table 4 - Comparison of cases of AUB according to age

Study / Age	Doraiswami et al [5] (2011)	Sawke et al [6] (2015)	Misra et al [7] (2017)	Uma et al [8] (2018)	Prathipaa et al [9] (2020)	Present study
<20	6 (1.5%)	-	-	-	1 (0.39%)	-
21-30	85 (20.8%)	14 (14%)	5 (1.2%)	25 (4%)	24 (9.38%)	55 (7.66%)
31-40	116 (28.4%)	30 (30%)	120 (30%)	117 (19%)	90 (35.16%)	265 (36.91%)
41-50	137 (33.5%)	41 (41%)	165 (41.25%)	345 (56.3%)	108 (42.19%)	283 (39.42%)
51-60	45 (11%)	15 (15%)	90 (22.5%)	88 (14.3%)	27 (10.55%)	71 (9.89%)
61-70	18 (4.4%)	-	20 (5%)	57 (9.5%)	6 (2.34%)	32 (4.46%)
71-80	2 (0.4%)	-	-	-	-	11 (1.53%)
91-100	-	-	-	-	-	1 (0.14%)
Total	409 (100%)	100 (100%)	400 (100%)	612 (100%)	256 (100%)	718 (100%)

In the present study, highest number of the AUB was seen in the multiparous women (84.11%) which is comparable to studies by Misra et al [7] (90%). Menorrhagia was the most common type of bleeding at the presentation (50.56%) in the present study, similar findings were noted in the studies by Singh et al[10](38.68%) and Kariappa et al (76.5%) [11].

Histopathological examination of the endometrium showed spectrum of patterns in which normal pattern (59.32%) was predominantly observed in reproductive age groups. It is comparable with the study by Sharma et al [12] which showed 62.19% cases of normal pattern endometrium.

Table 5- Comparison of cases of AUB according to histopathological pattern in various studies-

Histopathological findings \ Study		Doraiswami et al[5] (2011)	Sajitha et al [13] (2014)	Singh et al [10] (2016)	Revathy et al [14] (2017)	Bindroo et al [15] (2018)	Prathipaa et al [9] (2020)	Present study
Functional	Proliferative type endometrium	116 (28.36 %)	19 (12.2 %)	62 (29.25 %)	377 (62.8%)	93 (37.2%)	129 (50.39%)	358 (49.86%)
	Secretory phase endometrium		26 (16.7 %)	31 (14.62%)		85 (34%)	33 (12.89%)	69 (9.46%)
	Atrophic endometrium	10 (2.44 %)	8 (5.12 %)	34 (16.03%)	9 (1.5%)	18 (7.2%)	3 (1.17%)	74 (10.31%)
	Disordered proliferative type endometrium	84 (20.54 %)	19 (12.2 %)	-	57 (9.5%)	6 (2.4%)	8 (3.13%)	32(4.46%)
	Mixed pattern endometrium s/o hormonal imbalance		6 (3.84 %)		26 (4.3%)			26 (3.62%)
	Basal endometrium						-	11 (1.53%)
Organic	Endometritis	17 (4.16 %)	1 (0.64 %)	17 (8.02%)	3 (0.6%)	2(0.8%)	13 (5.08%)	49 (6.82%)
	Endometrial polyp	46 (11.25 %)	8 (5.12 %)	10 (4.72%)	22 (3.6%)	-	6 (2.34%)	35 (4.87%)
	Endometrial hyperplasia without atypia	25 (6.11 %)	39 (25 %)	44 (20.76%)	32 (5.4%)	40 (16%)	54 (21.09%)	23 (3.20%)
	Endometrial atypical hyperplasia						6 (2.34%)	4(0.56%)
	Endometrioid carcinoma	18 (4.4 %)	10 (6.42 %)	2(0.94%)	8 (1.3%)	4 (1.6)	1 (0.39%)	13 (1.81%)
	Serous carcinoma						-	1 (0.14%)
	Mucinous carcinoma						-	2 (0.28%)
Other	Inadequate		2 (1.28%)				-	21 (2.92%)
	Miscellaneous	93 (22.74 %)	18 (11.58%)	12 (5.66%)	66 (11%)	2 (0.8%)	3 (1.17 %)	
	Total	**409 (100%)**	**156 (100%)**	**212 (100%)**	**600 (100%)**	**250 (100%)**	**256 (100%)**	**718 (100 %)**

Proliferative pattern is the dominant histological pattern in our study which is comparable to study done by Prathipaa et al [9] (50.39 %). It is characterized by straight, simple tubular arrangement of glands. The stroma appears dense with spindle cells in early proliferative to edematous in mid proliferative to less edematous in late proliferative (Fig 1).

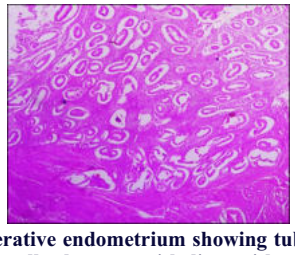

Fig 1 – Proliferative endometrium showing tubular endometrial glands lined by tall columnar epithelium with compact stroma. (H & E, x 4)

In the present study, atrophic endometrium was the second most common finding seen in 10.31 % of AUB cases whereas in Sajitha [13] et al and Bindroo et al [15] studies, secretory endometrium was the second most common finding which is characterized by thickening of wall and coiling of spiral arterioles In the study done by Singh et al [10], Bindroo et al [15] and Sajitha et al [13], atrophic endometrium was reported in 16.03%,7.2% and 5.12% cases respectively. The cause of bleeding in atrophic endometrium maybe due to anatomic vascular variations or local hemostatic mechanisms. Thin walled veins, superficial veins to the expanding cystic glands make vessel vulnerable to injury (Fig 2). All cases of atrophic endometrium were perimenopausal or post menopausal age group.

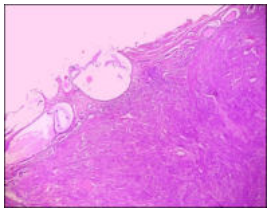

Fig 2 – Cystic atrophic endometrium (H & E, x 4)

Disordered proliferative endometrium (DPE) is an exaggeration of normal proliferative phase endometrium without significant increase in the overall ratio of glands to stroma and is due to persistent oestrogen stimulation. The absence of pattern uniformity is a principle defining feature of DPE which is a result of dyssynchronous growth of functionalis. [16] In our study, 32 cases, 4.46 % cases of DPE were observed which is comparable to Prathipaa et al (3.13%) while higher percentage were reported in the study done by Doraiswami et al [5] (20.54%), Sajitha et al [13] (12.2%) and Revathy et al [14] (9.5%). Disordered proliferative endometrium is a morphological bridge between normal proliferation and hyperplasia. [16] It is important to diagnose DPE at an early stage to prevent the disease progression.

In the present study among the organic causes, endometritis was the most common finding accounting for 49 cases (6.82%) which is comparable to studies done Singh et al [10] (8.02%) and Prathipaa et al [9] (5.08%). The diagnosis of chronic endometritis is made on the basis of presence of plasma cells and/or eosinophils (fig 3).

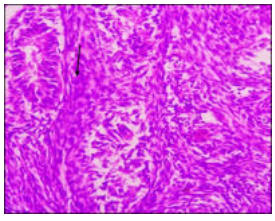

Fig 3 – Chronic endometritis showing infiltration by lymphocytes and plasma cells (arrow) within the endometrial stroma (H & E, x 40)

On gross examination, the polyp appeared as polypoidal fragments of tissue with epithelium on both sides. Narrow or broad stalk with fibrotic cut surface [16] (Fig 4 A). On microscopy, irregular endometrial glands along with endometrial stroma with thick walled blood vessels [16] (Fig 4 b). In the present study, endometrial polyp was seen in 4.87 % cases of AUB in the present study. Similar findings were demonstrated by Sajitha et al [13] and Singh et al [10]. The most common clinical presentation of the cases with endometrial polyp was continuous. PV bleeding while study done by Singh et al [10] observed menorrhagia as the most common clinical presentation.

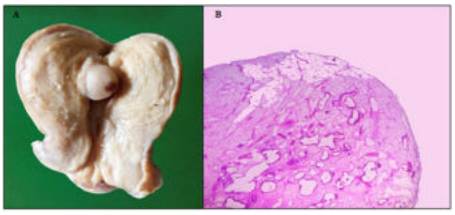

Fig 4 A) – Gross photograph of endometrial polyp showing polypoidal mass protruding into endometrial cavity. B) Endometrial polyp showing irregularly dilated endometrial glands surrounded by loose edematous stroma (H & E, x 4)

Endometrial hyperplasia was noted in 3.76 % cases of AUB. In contrast Sajitha et al [13], Singh et al [10] , Bindroo et al [15] and Prathipaa [9] reported higher number of cases. The possible reason could be higher percentage of cases with obesity and overweight patients in their studies. These factors lead to increased availability of peripheral estrogen due to excessive aromatization of androgens to estrogen in adipose tissue. It is important to diagnose endometrial hyperplasia because they are thought to be precursor of endometrial carcinoma. Endometrial hyperplasia without atypia is characterized by increased endometrial glands to stroma ratio with tubular, branching and / or cystically dilated glands without nuclear atypia (Fig 5 A). Endometrial hyperplasia with atypia / EIN can be distinguished on the basis of a combination of architectural features (glands crowding) and cytological features (altered epithelial cytology distinct from surrounding endometrium along with nuclear atypia and/ or entrapped non neoplasic glands). (Fig 5 B,C,D)

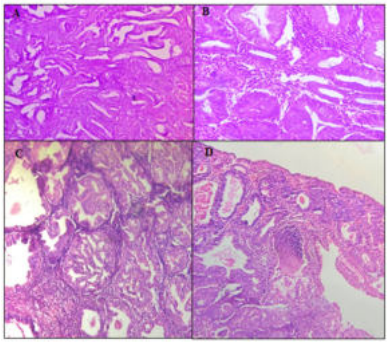

Fig 5 A: Endometrial hyperplasia without atypia (H & E, x10). B,C,D : Endometrial hyperplasia with Atypia / EIN (H & E, x 40)

Malignancies observed in this study included 13 cases of endometrioid carcinoma, two mucinous carcinoma and a single case of serous carcinoma. The distinction of Endometrical carcinoma from EIN is based on presence of stromal invasion (loss of intervening stroma), an altered endometrial stroma (desmoplastic stromal reaction) or a complex (mostly villoglandular architecture).

In the present study, the predominant type of endometrial carcinoma was endometrioid carcinoma which constituted 1.81% (13 cases) (Fig 6 A &B). However, a higher percentage of endometrial carcinoma was noted in Sajitha et al [13] (6.42%) and Doraiswami et al [5] (4.4%) studies. The possible explanation for higher percentage in these studies was predominance of cases in perimenopausal age group, nulliparity, increased BMI and chronic anovulation.

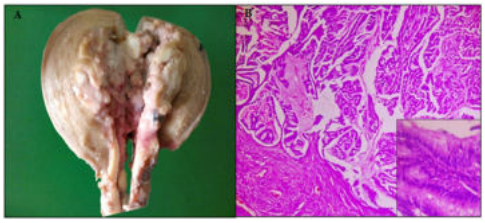

Fig 6 - A: Gross photography of Endometrioid carcinoma. B: Endometrioid carcinoma showing closely packed glands with back to back arrangement (H&E, x10).

In the present study, endometrial carcinoma was most commonly noted in post-menopausal period, similar findings were seen in Sajitha et al [13], Bindroo et al [15] and Doraiswami et al [5] studies. Similar to the study by Sajitha et al [13], the present study demonstrated post-menopausal bleeding as the most common presentation in cases of endometrioid carcinoma.In the present study, 2.88% of AUB cases were inadequate for opinion whereas Sajitha et al [13] reported it in only 1.28% of cases.

CONCLUSION –

Histopathological examination of endometrium in patients with abnormal uterine bleeding shows a wide spectrum of changes ranging from normal endometrium in various hormonal cycles to malignancy. AUB needs thorough and prompt evaluation as it could be the only clinical manifestation of serious underlying condition like endometrial cancer. The present study highlights the importance of histopathological examination of endometrium which plays a pivotal role in the management of AUB. Hence, histopathological examination and its correlation with clinical history still remains gold standard for diagnosis of AUB.

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