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Clinicopathological study of the endometrium in patients with abnormal uterine bleeding: A descriptive study

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Abstract

Introduction: Abnormal uterine bleeding (AUB) is the commonest presenting symptom and major gynecological problem responsible for as many as one-third of all out patient gynecologic visit. Diagnosis and management strategies of AUB is not complete without histopathological characteristics of endometrial biopsy material and hysterecrtomy specimens.

Aims and Objectives

1. To study clinical presentation in patients of various age groups with abnormal uterine bleeding, in a period of two years.
2. To study the histopathology of the endometrium in patients with abnormal uterine bleeding.

Materials And Methods: Total 250 patients of all age groups who presented with AUB were studied. The study included endometrial curettings or biopsy and hysterectomy specimens.

Results: The commonest age group affected was 41-50 years followed by 31-40 years. In age group of 31- 40 years, 41-50 years and 51-60 years most common histopathological finding was endometrial hyperplasia in 10 cases (22.73%), 44 cases (30.13%) and 11 cases (30.56%) respectively. Majority of the cases presented with heavy menstrual bleeding upto the age group of 50 years. Most common presentation in the age group above 50 years was postmenopausal bleeding. The difference in clinical and histopathological diagnosis by PALMCOEIN classification was statistically significant in groups of AUB(M), AUB(O) and AUB(E) with p value 0.0001, except AUB (P) as the diagnosis was same clinically as well as histopathologically in all 18 cases.

Majority 47(40.17%) cases of endometrial thickness (ET) 11-15 mm had endometrial hyperplasia. The consistency rate of histopathological diagnosis of endometrium between endometrial biopsy and hysterectomy specimens was 74.77% and there was 25.23% discordance between them.

Conclusion: An accurate histopathological diagnosis facilitates the implementation of optimal treatment

strategies and unnecessary radical surgery may be avoided.

Keywords: Abnormal uterine bleeding, Endometrial biopsy, Heavy menstrual bleeding

Introduction

Abnormal uterine bleeding is defined as any bleeding pattern that differs in regularity, frequency of menses, duration of flow and amount of blood loss from a pattern observed during a normal menstrual cycle or menopause.1 It is the commonest presenting symptom and major gynecological problem responsible for as many as one-third of all out patient gynecologic visits.2 Causes of AUB may be physiological, pathological or pharmacological.3 AUB is a collective terminology that includes both structural (organic) and functional (non-organic) causes. Common structural causes include endometrial polyps, adenomyosis, leiomyoma, endometrial hyperplasia and carcinoma. The functional disturbances referred to Dysfunctional Uterine Bleeding, which is a subgroup of AUB are caued by anovulation.4,5 A new classification for the causes of abnonormal uterine bleeding (AUB) is based on the acronym PALM- COEIN- polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified, was developed by the International Federation of Gynaecology and Obstetrics (FIGO) in 2011. In general, the components of the PALM group are structural entities that can be measured visually with imaging techniques and/ or histopathology, whereas the COEIN group is related to the functional disturbances, referred to as Dysfunctional Uterine Bleeding (DUB). The term ―DUB, is not included in the system and should be abandoned, as per the agreement process.6 Abnormal uterine bleeding manifests in a wide range of presentations as irregular menstrual bleeding, amenorrhea, oligomenorrhea, light menstrual bleeding, heavy menstrual bleeding, heavy and prolonged menstrual bleeding, frequent bleeding, intermenstrual or post-coital bleeding, and postmenopausal bleeding.7 According to FIGO, recommended terminologies, of symptoms of AUB are Heavy Menstrual Bleeding (HMB) for menorrhagia, Inter menstrual bleeding (IMB) for metrorrhagia, Heavy and Prolonged Menstrual Bleeding (HPMB) for menometrorrhagia, Frequent menstrual bleeding (FMB) for polymenorrhagia and Infrequent Menstrual Bleeding (IFMB) for Oligomenorrhea.8 It is associated with almost any type of endometrium ranging from normal endometrium to hyperplasia, irregular ripening, chronic menstrual irregular shedding and atrophy.9 Diagnosis and management strategies of AUB is not complete without histopathological characteristics of endometrial biopsy material.10 Endometrial biopsy taken by dilatation and curettage, remains the standard diagnostic procedure for the diagnosis of endometrial pathology.[11]

Materials And Methods

Study design- This was a descriptive, cross sectional study.

Study period- This study was conducted for a period of 2 years.

Place of research- This study was carried out in the Department of Pathology.

Ethical considerations- The study was approved by the Institutional Ethics Committee of the Tertiary Care Institute. Informed consent form was taken from the participants.

Sample size- Total 250 patients of all age groups with complaints of abnormal uterine bleeding who presented at the Department of Obstetrics and Gynaecology,

Tertiary Care Institute during the study period were studied.

Inclusion criteria- Patients presenting with endometrial causes of AUB of all age groups were included in the study.

Exclusion criteria- Patients with cervical, vaginal, predominantly myometrial pathology (leiomyoma, adenomyosis) and known gestational causes were excluded from the study.

Methodology- Detailed clinical history was collected from patients along with relevant investigations. Endometrial biopsy/ curetting samples from all the 250 patients who presented with AUB were collected. Out of these 250 cases,107 patients who either did not respond to the medical management or had thickened endometrium on TVS and who had completed their family or diagnosed histologically on endometrial biopsy as atypical hyperplasia or carcinoma, underwent hysterectomy. All these specimens were immediately put in 10% formalin and received in the Pathology Department for evaluation. The gross features of the specimen were examined and noted. Total submission of endometrial biopsy/ curettings and representative sections from hysterectomy specimens were processed routinely. Paraffin tissue blocks were prepared, 4-6µ thick sections were cut and stained with routine Hematoxylin and Eosin (H & E) stains. Special stain such as Zeihl- Neelsen stain was used as per the case requirement. Histopathological examination under light microscope were carried out and the findings were recorded.

Statistical analysis: All the collected data was entered in Microsoft Excel. Statistical analysis was done by compiling and tabulation of data by using EPIINFO 7.2 version. The qualitative data was expressed in terms of percentage and quantitative data in terms of mean and standard deviation. Chi square test was used for comparing clinical and histopathological diagnosis by PALM-COEIN classification. A p value less than 0.05 was considered to indicate statistically significant association.

Results

According to age, majority 146 cases (58.40%) were in age group of 41-50 years followed by 44 cases (17.60%) in age group of 31-40 years. The mean age was 44.84±8.63 years ranging between 18-75 years.

According to type of bleeding in AUB, majority 104(41.60%) cases had heavy menstrual bleeding followed by Intermenstrual bleeding in 47(18.80%).Postmenopausal bleeding was seen in 40(16%) cases.

Majority 148 cases (59.2%) had parity 2 followed by parity 1 in 50 cases (20%). 16 cases (6.4%) were nulliparous.

According to endometrial thickness (ET) on TVS majority 117 cases (46.80%) had ET of 11-15 mm followed by 83 cases (33.20%) with ET of 5-10 mm. Only 11 cases (4.40%) had ET >20 mm.

Functional causes were seen in maximum 143 cases (57.20%) followed by organic causes in 107 cases (42.8%).

Table 1: Distribution of study subjects according to functional causes of AUB

Functional causes of AUB	N(%)
Proliferative phase	55 (38.46)
Secretory phase	43 (30.07)

Menstrual phase	06 (4.20)
Disordered proliferative endometrium	18 (12.58)
Atrophic endometrium	06 (4.20)
Hormone effect	15 (10.49)
Total	143 (100)

In Table 1, out of total 143 cases of functional causes, proliferative phase was seen in maximum 55 cases (38.46%) followed by secretory phase in 43 cases (30.07%). Disordered proliferative endometrium was seen in18 cases (12.58%)

Table 2 : Distribution of study subjects according to organic causes of AUB

Organic causes of AUB	N(%)
Chronic nonspecific endometritis	04(3.74)
Tuberculous endometritis	02(1.87)
Endometrial polyp	18(16.82)
Endometrial hyperplasia	71(66.35)
Endometrial carcinoma	10(9.35)
Carcinosarcoma (MMMT)	02(1.87)
Total	107(100)

Table 2 shows distribution of cases according to organic causes of AUB. Out of total 107 cases of organic causes, endometrial hyperplasia was seen in maximum 71 cases (66.35%) followed by endometrial polyp in 18 cases (16.82%). Endometrial carcinoma was seen in 10 cases (Only 10 cases (9.35%) had endometrial carcinoma and 02(1.87%) had carcinosarcoma (Malignant mixed Müllerian tumour-MMMT).

Table 3 : Distribution of study subjects on histopathological diagnosis by PALM-COEIN classification

Histopathological diagnosis	PALM-COEIN classification	Total N (%)
Proliferative phase	AUB(E)	55(22.00)
Secretory phase	AUB(E)	43(17.20)
Menstrual phase	AUB(E)	06(2.40)
Disordered proliferative endometrium	AUB(E)	18(7.20)
Atrophic endometrium	AUB(E)	06(2.40)
Hormone effect	AUB(I)	15(6.00)
Chronic nonspecific endometritis	AUB(E)	04(1.60)
Tuberculous endometritis	AUB(E)	02(0.80)
Endometrial polyp	AUB(P)	18(7.20)

Endometrial hyperplasia	AUB(M)	71(28.40)
Endometrial carcinoma	AUB(M)	10(4.00)
Carcinosarcoma (MMMT)	AUB(M)	02(0.80)
Total		250(100)

Table 3 shows majority of AUB cases on histopathological diagnosis by PALM-COEIN classification were in AUB-E group (Proliferative phase, Secretory phase, Menstrual phase, Disordered proliferative endometrium, Atrophic endometrium, Chronic nonspecific endometritis, Tubercular endometritis).

On correlation between clinical and histopathological diagnosis, the diagnosis of AUB (P) was same in all 18 cases. In other classes including AUB(M), AUB(O) and AUB(E) there was difference in clinical and histopathological diagnosis and it was found to be statistically significant (p value in each group was 0.0001). The difference in clinical and histopathological diagnosis of AUB(I) was not significant (p value = 0.55).

Table 4: Correlation of histopathological diagnosis with type of bleeding in AUB

Histopathological diagnosis	Type of bleeding						Total
	HMB	IMB	HPMB	FMB	IFMB	PMB	
Proliferative phase	31(29.81)	11(23.40)	07(26.92)	01(5.56)	02(13.33)	02(5.00)	55(22.00)
Secretory phase	20(19.23)	05(10.64)	04(15.38)	03(16.66)	06(40.00)	05(12.50)	43(17.20)
Menstrual phase	02(1.92)	01(2.13)	02(7.69)	01(5.56)	01(6.67)	00(00)	06(2.40)
Disordered proliferative endometrium	09(8.65)	01(2.13)	03(11.54)	02(11.11)	02(13.33)	01(2.50)	18(7.20)
Atrophic endometrium	00(00)	00(00)	00(00)	00(00)	00(00)	06(15.00)	06(2.40)
Hormone effect	10(9.62)	01(2.13)	02(7.69)	02(11.11)	00(00)	00(00)	15(6.00)
Chronic nonspecific endometritis	00(00)	03(6.38)	00(00)	01(5.56)	00(00)	00(00)	04(1.60)
Tuberculous endometritis	01(0.96)	00(00)	01(3.85)	00(00)	00(00)	00(00)	02(0.80)
Endometrial polyp	05(4.81)	07(14.89)	02(7.69)	02(11.11)	00(00)	02(5.00)	18(7.20)

Endometrial Hyperplasia	25(23.30)	18(38.30)	05(19.23)	06(33.33)	04(26.67)	13(32.50)	71(28.40)
Endometrial carcinoma	01(0.96)	00(00)	00(00)	00(00)	00(00)	09(22.50)	10(4.00)
Carcinosarcoma (MMMT)	00(00)	00(00)	00(00)	00(00)	00(00)	02(5.00)	02(0.80)
Total	104(100)	47(100)	26(100)	18(100)	15(100)	40(100)	250(100)

In Table 4, out of total cases of HMB, 31 cases (29.81%) were in proliferative phase. There were 18 cases (38.30%) of IMB in endometrial hyperplasia category and 11 cases (23.40%) in proliferative phase. 7 cases (26.92%) of HPMB were in proliferative phase. Most common diagnosis in FMB was endometrial hyperplasia in 6 cases (33.33%). 6 cases (40%) of IFMB were in secretory phase. Atrophic endometrium was seen only in those who presented with PMB in 6 cases (15%).

Table 5 : Correlation of histopathological diagnosis with endometrial thickness on TVS

Histological diagnosis	Endometrial thickness (in mm)					Total
	<5	5-10	11-15	16-20	>20	
Proliferative phase	04(40.00)	25(30.12)	25(21.37)	01(3.45)	00(00)	55(22.00)
Secretory phase	03(30.00)	22(26.51)	17(14.53)	01(3.45)	00(00)	43(17.20)
Menstrual phase	00(00)	06(7.23)	00(00)	00(00)	00(00)	06(2.40)
Disordered proliferative endometrium	00(00)	07(8.43	11(9.40)	00(00)	00(00)	18(7.20)
Atrophic endometrium	03(30.00)	03(3.61)	00(00)	00(00)	00(00)	06(2.40)
Hormone effect	00(00)	08(9.64)	07(5.98)	00(00)	00(00)	15(6.00)
Chronic nonspecific endometritis	00(00)	03(3.61)	01(0.85)	00(00)	00(00)	04(1.60)
Tuberculous endometritis	00(00)	00(00)	02(1.71)	00(00)	00(00)	02(0.80)
Endometrial polyp	00(00)	01(1.20)	07(5.98)	10(34.47)	00(00)	18(7.20)
Endometrial Hyperplasia	00(00)	08(9.65)	47(40.17)	16(55.18)	00(00)	71(28.40)
Endometrial	00(00)	00(00)	00(00)	01(3.45)	09(81.82)	10(4.00)

carcinoma						
Carcinosarcoma (MMMT)	00(00)	00(00)	00(00)	00(00)	02(18.18)	02(0.80)
Total	10(100)	83(100)	117(100)	29(100)	11(100)	250(100)

Table 5 shows majority 47(40.17%) cases of endometrial thickness (ET) 11-15 mm had endometrial hyperplasia with mean ET of 13.52 ± 2.44 mm. Mean ET in proliferative phase was 9.90±3.35 mm. Mean ET in endometrial malignancy cases (endometrial carcinoma and carcinosarcoma) was 22.16±1.58. Majority 16 cases (55.18%) with ET of 16-20 mm and 9 cases (81.82%) with ET >20 mm had endometrial hyperplasia and endometrial carcinoma respectively.

Table 6 : Discordance in endometrial biopsy histopathology with the endometrial histopathology after hysterectomy

Total number of cases with discordance	Histopathology diagnos on endometrial biopsy	Histopathology diagnosis on hysterectomy
5	Proliferative phase	Secretory phase
3	Secretory phase	Proliferative phase
2	Proliferative phase	Disordered proliferative endometrium
1	Hyperplasia without atypia	Proliferative phase
1	Atypical hyperplasia	Hyperplasia without atypia
1	Secretory phase	Hyperplasia without atypia
1	Disordered proliferative endometrium	Hyperplasia without atypia
1	Hyperplasia without atypia	Tuberculous endometritis
3	Hyperplasia without atypia	Endometrial polyp
5	Hyperplasia without atypia	Atypical hyperplasia
2	Atypical hyperplasia	Endometrial carcinoma
1	Atypical hyperplasia	Carcinosarcoma
1	Endometrial carcinoma	Carcinosarcoma
Total- 27		

In Table 6, out of total 107 cases of hysterectomy specimens, 27 cases 25.23% had discordance in histopathological diagnosis with endometrial biopsy. There was 74.77% (80/107) concordance in histopathological diagnosis of endometrial biopsy and hysterectomy specimens.

Discussion

AUB is a common condition accounting for 25% of gynecological operations and 20% of outpatient visits. The diagnosis is different among various age groups and histopathological examination helps in diagnosis.2 An accurate histopathological diagnosis facilitates the implementation of optimal treatment strategies and unnecessary radical surgery may be avoided.12 Similar to the present study, studies by Jairajpuri et al13 , Moradan et al14 from Iran, Rajagopal et al15 also found majority of cases in age group of 41-50 years. Studies like Mahmoud et al16 from Iraq (42.7%),

Jairajpuri et al13 (41%), Arnold et al17 (43.7%), Verma R et al18 (40%), had majority of cases presenting with HMB (menorrhagia) which is, similar to present study (41.6%). Sheelakshmi U et al19 and Betha et al20 and Ibrahim et al21 from Egypt showed highest incidence with parity 2 similar to the present study. We had majority of cases with endometrial thickness between 11-15 mm with incidence of 46.80% which is in concordance with studies done by Shrestha P et al22 and Singh M et al23 with incidence of 48.5% and 50% respectively. In the present study, out of total 250 cases, majority of cases were due to functional causes (no definite structural pathology) in 143 cases (57.25%) and organic causes (pathological changes) were noted in 107 cases (42.8%) which is similar to studies of Mirza T et al24, Ghani et al25 and Bolde et al.26 In our study, the commonest histopathological finding among functional causes, was proliferative phase with incidence of 38.46% consistent with Studies of Chitra et al27 and Deka R et al.28 Among organic causes, the commonest histopathological finding was endometrial hyperplasia with incidence of 66.35% which is consistent with studies of Devi Junu et al29 and Patel H et al.30 Histopathology helped us in accurate diagnosis of causes of AUB missed on clinical diagnosis. As per PALMCOEIN classification, all the 18 cases of AUB-P, 12 cases of AUB-M and 12 cases of AUB(I) diagnosed clinically were confirmed on histopathology as Endometrial polyp (AUB-P), Endometrial carcinoma (AUB-M) and Hormone effect (AUB-I) with additional 3 cases of AUB(I) reported on histopathology. The causes of AUB which were misdiagnosed clinically as AUB-O were diagnosed on histopathology as AUB-M (Endometrial hyperplasia), AUB-E (Proliferative phase, Secretory phase, Disordered proliferative endometrium, Atrophic endometrium, Chronic non specific endometritis and Tuberculous endometritis) and 3 cases of AUB-I (Hormone effect). In the present study, the difference in clinical and histopathological diagnosis of AUB(I) was not significant (p value = 0.55). There was significant difference in clinical and histopathological diagnosis by PALM-COEIN classification in groups of AUB(M), AUB(O) and AUB(E) except AUB (P) as the diagnosis was same clinically as well as histopathologically in all 18 cases. A similar study by Betha et al20 found similar results in clinico-histopathological correlation of AUB cases. Their —p value was 0.003 in PALM-COEIN classification. In our study, the —p value was 0.0001. Mishra et al31 noted significant difference in clinical and histopathological diagnosis for AUB (E), AUB (M). But there was no significant difference in cases of AUB (P) and AUB (O). Pillai et al32 and Ghanbarzadeh et al33 from Iran found that out of total cases of menorrhagia (heavy menstrual bleeding), majority of cases were in proliferative phase and this was similar to present study findings. Varun N et al34 found that, in patients who presented with menorrhagia (heavy menstrual bleeding), proliferative endometrium was the most common finding. Endometrial carcinoma presented as menorrhagia in 2 cases and postmenopausal bleeding in remaining 2 cases, which are consistent with our study. In the present study, majority 47(40.17%) cases of endometrial thickness 11-15 mm had endometrial hyperplasia with mean thickness of 13.52 ± 2.44 mm. Mean endometrial thickness in endometrial malignancy cases (endometrial carcinoma and carcinosarcoma) was 22.16±1.58. Similar findings regarding mean ET for endometrial hyperplasia and carcinoma was observed by Krishnamoorthy et al35, Van Den Bosch et al36 and Rusell et al.37 The present study showed 74.77%

concordance in histopathology of endometrial biopsy or curettage and hysterectomy specimens which is close to the study by Hemida et al38 from Egypt who observed the concordance rate as 79.5%. A study by Singh P et al39 and Obeidat et al40 from Jordan observed the consistency rate of histopathology findings among endometrial curettage and hysterectomy samples as 56.25% and 45.5% respectively, which is lower than present study. According to McCluggage41 one of the most common lesion to be misdiagnosed as hyperplasia is an endometrial polyp, especially when this is removed piecemeal, and when the gynaecologist is not aware of the presence of a polyp and the suggestion of which is not conveyed to the pathologist. We also misdiagnosed 1 case of endometrial polyp as hyperplasia without atypia on endometrial biopsy. We had missed one case of tuberculous endometritis on endometrial biopsy which was picked up on histopathology of the hysterectomy specimen. Tuberculous endometritis can be undiagnosed on endometrial biopsy or curettings if only a few tubercles exist and are localized to a small fragment of the curettings not included in the plane of section. Clinically, when there is a suspicion for tuberculosis or when a chronic endometritis exists without any cause, then the paraffin block should be sectioned at deeper levels and all the tissue fragments should be looked carefully for a possible tuberculous granuloma.42 Kleebkaow P et al43 noted that 6.3% cases of endometrial hyperplasia diagnosed by curettage had more severe histology (like atypical hyperplasia and carcinoma) from hysterectomy specimens. Thus, it is necessary to take repeated curettage or other investigations should be carried out in women with recurrent bleeding.

Conclusion

The endometrial biopsy by curettage had good diagnostic yield. Persistent uterine bleeding unresponsive to medical management after curettage indicates the presence of lesions such as hyperplasia, particulary atypical hyperplasia and a focus of carcinoma in hyperplastic endometrium and needs hysterectomy. Thus, a thorough histopathological work up and clinical correlation is necessary in cases of abnormal uterine bleeding.We concluded that preoperative endometrial sampling had good histological correlation to hysterectomy specimens.

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Legend Figure

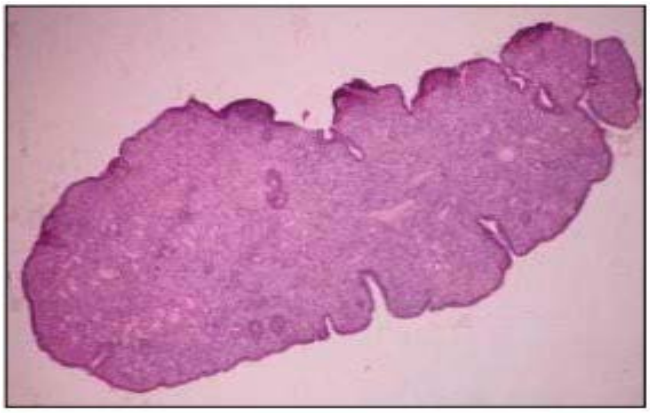

Figure 1: Photomicrograph of endometrial polyp lined by cuboidal epithelium, composed of irregular dilated endometrial glands lined by pseudostratified columnar cells with dense fibrotic stroma containing thick walled blood vessels (Hematoxylin and eosin stain 10x)

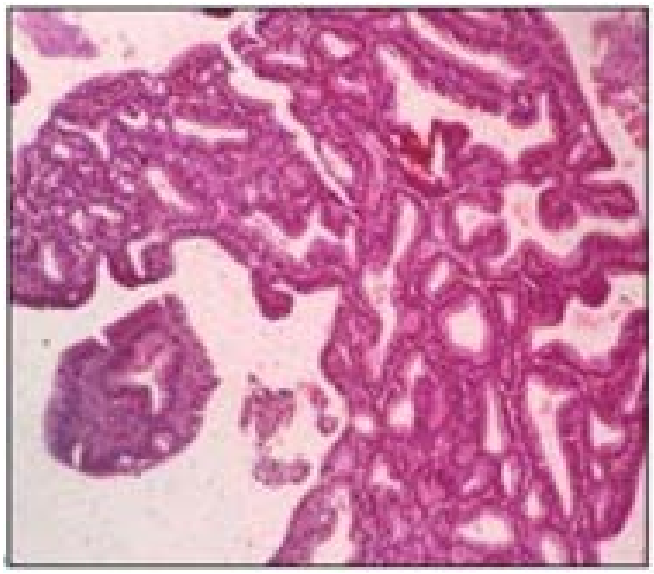

Figure 2: Photomicrograph of well-differentiated endometrial (endometrioid type) carcinoma (FIGO grade 1) composed of irregular glands showing papillary architecture, lined by pseudostratified columnar epithelial cells with large, round, hyperchromatic nuclei showing mild anisonucleosis and pleomorphism with very scanty intervening fibroconnective stroma and contains < 5% of overall solid areas (Hematoxylin and eosin stain 10x)

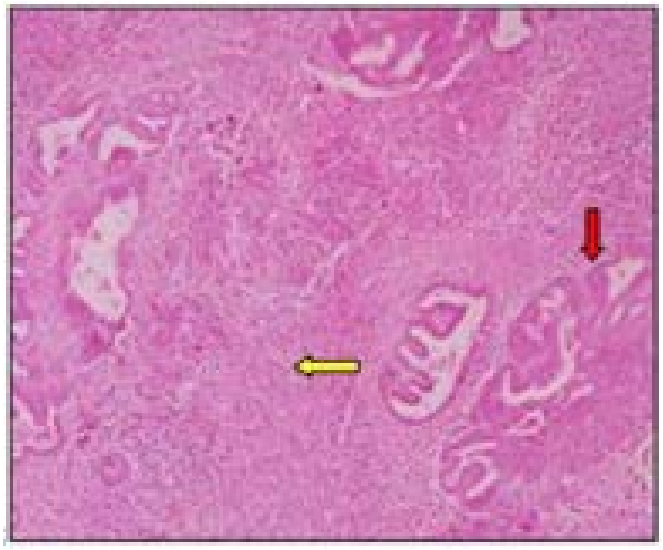

Figure 3: Photomicrograph shows carcinosarcoma (malignant mixed mullerian tumour) of uterus composed of moderately differentiated carcinomatous (glandular) shown by thick red arrow and sarcomatous

(endometrial stromal) components shown by thin yellow arrow, (Hematoxylin and eosin stain 10x)