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Spectrum of Histopathological Diagnosis of Uterine Lesions in Patients of Abnormal Bleeding

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ABSTRACT:

Menstrual problems are very common in females of reproductive age, which cause a significant burden on society and the family with frequent visits to medical facilities.Abnormal uterine bleeding (AUB) is a symptom not a disease. It accounts for more than 70% of all gynaecological consultants in the peri-and postmenopausal age groups. As different abnormal and normal endometrial pathologies are encountered with diagnostic challenges for histopathologists in patients with abnormal uterine bleeding. Nowadays, ultrasonography (USG) is preferred over dilatation and curettage (D&C) as non-invasive. However, in small health centres such as primary health care in rural areas where ultrasonography (USG) is not available, D&C delivers the same results in such settings. The present study is therefore required to correlate these histopathological findings with transvaginal ultrasound (TVUS) in D&C and/or hysterectomy specimens, in addition to the accuracy of TVUS, which is used as a screening tool.

KEYWORDS: *hyperplasia, carcinoma, menorrhagia, ultrasonography, transvaginal ultrasound.*

INTRODUCTION:

Menstrual diseases are a common manifestation of the need for medical visits among women of severe menstrual bleeding of procreative age.[1] There is a significant health care burden on society and the family due to abnormal uterine bleeding in females.

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This causes an impact on the quality of life that occurred during off-time work, resulting in a variety of surgical procedures and ultimately having a significant effect on the health care system.[1]Abnormal uterine bleeding is a symptom, not a disease. [2] It accounts for more than 70% of all gynaecological conditions in the peri-and post-menopausal age groups. [3] The estimated worldwide prevalence of subjective, self-defined AUB varies greatly, from 4 to 52%. [4] In India, AUB is reported to occur between 9 and 14 % of menarchal and menopausal women. India has an AUB prevalence of approximately 17.9 %.[5]

The International Federation of Gynaecology and Obstetrics (FIGO) suggested terminology for abnormal uterine bleeding to rationalize terminologies such as metrorrhagia, menorrhagia and dysfunctional uterine bleeding. Abnormal uterine bleeding is defined as any variation in the normal menstrual cycle and includes changes in menstrual regularity and frequency, duration of flow, or amount of blood loss. Sub-categories of abnormal uterine bleeding based on frequency, amount of menstrual blood, duration, regularity, chronicity and timing of reproductive status have again been further divided.[6]

FIGO workshop group had created the new classification for the causes of abnormal bleeding which is known as **PALM- COEIN**.[6]FIGO system of classification is divided into nine categoriesthat are known as **P** stands for Polyp, **A** stands for Adenomyosis, **L** stands for Leiomyoma, **M**stands forMalignancy and hyperplasia, **C** stands for Coagulopathy, **O** stands for Ovulatory dysfunction, **E** stands for Endometrial disorder, **I**standsfor Iatrogenic and **N** stands forNot yet classified. The first group consists of structural abnormalities disorders that are easily determined by the use of radiological procedures as well as histopathological examination, while the second group consists of non-structural abnormalities that are not well described by radiological procedures or histopathology. [7]

Aetiology of AUB is divided into physiological and pathological causes, where the former involves a decrease in oestrogen levels following the follicular phase peak, which allows the endometrium to be shed and has organic causes, including genital tract infections, benign tumours such as fibroid, polyp, pre-malignant lesions such as endometrial hyperplasia and malignant tumours such as endometrial carcinoma[8]; anovulation or oligo-ovulation [8]accountable for 80% of menorrhagia[9]; medications also cause abnormal uterine bleeding likeanti-coagulants, anti-depressants(selectiveserotoninreuptakeinhibitors: SSRIs),[10]Tamoxifen, hormonal contraceptives, Anti-psychotics(first generation and Risperidone),[11] [12]corticosteroids, herbs : ginseng [13]chasteberry, [14]and danshen. [15] Complications related to abnormal uterine bleeding are perforation, usually followed by obstetric and gynaecological surgery, while others are infection and haemorrhage. AUB may also be a consequence of genito-urinary tract cancer. [16]

Diagnosis of AUB and its underlying cause is very important for the planning of appropriate treatment. In addition to patient age and history, various laboratory values such as pregnancy tests, complete blood count, platelet count, coagulation profile, sex steroid hormone levels (progesterone, oestrogen, androgens), thyroid function tests, prolactin levels, gonadotropin

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levels should be estimated (FSH, LH). [17] The imaging techniques that can be used for AUB analysis are TVUS, saline infused sono-hysterography (SIS), hystero-salpingo-graphy (HSG) etc. Transvaginal ultrasonography (TVUS) is a relatively cheaper and non-invasive technique for the direct assessment of pelvic organs and endometrial thickness. [18] There is a better visualization of the endometrium and the uterus as a result of the positioning of the high-frequency ultrasound transducer closer to the region of interest. [19]

Saline infused sono-hysterography (SIS) is a modified TVS method that allows us to visualize uterine abnormalities more clearly by cutting the walls of the uterine cavity apart by injecting salt into the cavity. [20]Other diagnostic modalities such as hysterosalpingography (HSG) may also be used where the fallopian tube patency is assessed and considered to be a gold standard. The best possible time for endometrial evaluation is the early proliferative phase due to the optimal visualization of the endometrial cavity. [21]Although dilatation and curettage (D&C) is a standard procedure for diagnosing endometrium histological assessment for early detection of premalignant lesions of the female genital tract, in particular endometrial atypical hyperplasia; but the disadvantage of this technique is that it cannot diagnose focal benign lesions of endometrium and myometrium such as leiomyomas, endometrial polyp and adenomyosis as it is a blind procedure. [18][22]

Nowadays, USG is preferred over D&C as a non-invasive technique. However, in small health centres such as primary health care in rural areas where USG is not available, D&C delivers the same results in this setting. The present study is therefore required to correlate these histopathological findings with TVUS in D&C and/or Hysterectomy specimens, in addition to the accuracy of TVUS, which is used as a screening tool. With TVUS, D&C remains a very practical, reliable and cost-effective approach to the investigation of AUB. Appropriate histopathological diagnosis is achieved in the implementation of the treatment. The study was therefore conducted to correlate clinic-pathological findings, histopathological endometrial diagnosis, with those of transvaginal-sonographic findings.

DISCUSSION:

Abnormal uterine bleeding is one of the most common clinical conditions experienced by more than 20% of women worldwide in the outpatient gynaecology department. It is a significant debilitating health problem for rural women as it is considered stigmatizing and also due to lack of adequate facilities. Proper diagnosis must therefore be made in order to ensure adequate treatment and better survival of women of reproductive age and to reduce the debilitating condition that affects the quality of life.

Evaluation of these patients on the basis of clinical history, complaints followed by radiological investigations such as ultrasonography and transvaginal sonography play a very important role. These investigations are only screening methods and provide a rough idea of the underlying cause. The histopathological examination of the tissue sample taken by dilatation and curettage must be further confirmed. However, in order to be more precise, endometrial biopsy should be performed to include the smallest possible pathological tissue without being missed.

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According to a study conducted by **Machado et al.**, [23] proliferative endometrium was the most common finding in histopathological examination, which was approximately 44.37% in 71 patients followed by secretary endometrium. No statistically significant association was found between endometrial thickness and cycle day with histopathology. Atypia or malignancy has not been found in women with an endometrial thickness of <5 mm and hence, curettage can be avoided in such cases. Transvaginal-sonography is good initial screening tool in the evaluation of women with abnormal uterine bleeding.

Pyari et al., [24] concluded that the most common symptoms in patients with abnormal uterine bleeding were menorrhagia (40%), metrorrhagia (18%), menometrorrhagia (14 %) and poly-menorrhea (14%). Compared to hysteroscopy; TVS had a sensitivity of 86% and a specificity of 31%, PPV of 78%, NPV of 44%, while D&C had a sensitivity of 89% and a specificity of 45%. They also concluded that hysteroscopy and guided biopsy are more sensitive than TVS or D&C in the diagnosis of abnormal uterine bleeding.

The **Pacarada et al.**[25] study group concluded that more than 30% of the patients with endometrial thickness between 3 and 10 mm showed no pathological changes. Histopathological findings revealed polyposis, hyperplasia, carcinomas and other pathological abnormalities in patients with an endometrial thickness of more than 10 mm. Among 120 patients, 23% had atypical hyperplasia and 5% had endometrial carcinoma. The study concluded that the use of transvaginal sonography in combination with histopathological examination of D& C could improve the selectivity of the endometrium assessment in postmenopausal women as well as the accuracy of pathological findings.
Results of the study conducted by **Bhatta et al.**, [26]showed predominant endometrial histopathological finding of proliferative endometrium in 32 cases (26.23 %) followed by simple hyperplasia without atypia in 22 cases (18.03%). Malignant lesions were more common in patients >40 years of age and included in 7 cases (5.74%). Atrophic endometrium was most common in post-menopausal bleeding 8 cases (28.6%) followed by endometrial carcinoma 5 cases (17.9%). The study concluded that the histopathological examination of endometrium should be carried out generously in women with abnormal uterine bleeding, especially after 40 years of age, in order to rule out malignancies.

In a study conducted by **Kaur et al.** [27], 5.71% of cases of endometrial adenocarcinoma were reported. No case of abnormal high-risk type of endometrium with an endometrial thickness of less than 4 mm was diagnosed. The sensitivity and specificity of transvaginal sonography as a screening modality was 100% and 72.73% respectively. The study concluded and validated the use of transvaginal sonography as a screening tool for post-menopausal bleeding patients.

Endometrial lesions detected by **Kaul I et al.**, [28] via histopathology were hormonal effects (proliferative and secretory endometrium) in 5 cases (10%), endometrial polyps in 4 (8%), endometritis in 2 (4%), endometrial hyperplasia in 9 (18%) and endometrial carcinoma in 5 (10%). A total of 21 cases (42%) had atrophic endometrium and 4 (8%) had an inadequate sample. On TVS, 24 (48%) women had endometrial thickness (ET) < 5 mm and 26 (52%)

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women had endometrial thickness (ET) < 5 mm. At a cut-off limit of > 5 mm for endometrial thickness indicating pathological endometrium, the sensitivity and specificity of TVS was 100% and 80%, respectively, and the predictive value was a positive test, with a negative test and accuracy of 76.9%, 100% and 89% respectively. This study shows that TVS allows the detection of endometrial pathology in the vast majority of women and is relatively easy, cheap, non-invasive and does not require anaesthesia. It can be used as the first diagnostic step in the investigation of postmenopausal bleeding women.

Deshmukh etal., [29]investigated the sensitivity, specificity, PPV and NPV of TVS for diagnosis of various menstrual phases. The values obtained were as follows: 92.64%, 100%, 100% and 88% (proliferative phase), 100%, 89.77%, 70% and 100% (secretory phase), 76%, 100%, 100%, 95.60% (hyperplasia)and 100%, 100%, 100%, 100% (menstrual phase).They concluded that TVS should be the first line of choice in the diagnosis and management of DUB, as it is non-invasive, inexpensive and convenient for the patient. When endometrial thickness is 14mm and above, endometrial healing and histopathology should be followed by TVS to rule out endometrial pathology.

The study conducted by**Gupta etal.,** [30]concluded that the maximum frequency of abnormal uterine bleeding was seen in age groups 40–45 years. The average age range was 45.74 ± 2.81 years. Most of the patients were para 3. Menorrhagia was the most common complaint and fibroid uterus was responsible for abnormal uterine bleeding in 53% of women. Out of 39 women clinically labelled as dysfunctional uterine bleeding, 8 patients were diagnosed with fibroid uterus and no organic cause was found in the rest of the 31 patients. Out of these 31 patients, 4 patients were diagnosed as adenomyosis on histopathological evaluation. No gross abnormality was observed in the remaining patients.Three cases which were suspicious for malignancy were confirmed by histopathological assessment. Simple endometrial hyperplasia without atypia was present in 19% of patients. They concluded that clinical, radiological and pathological assessment was well correlated with the diagnosis of fibroids, although clinical evaluation and USG ultrasound were shown to be of little help in the diagnosis of adenomyosis.

Pillai et al., [31] came up with the results, 40% of patients were 48 to 51 years of age and 46.5 % had menstrual menorrhagia complaints, which accounted for the most common menstrual complaint. 70.5 % of the patients in the study group were in para 2 or less. Fibroid uterus was the most common uterine pathology detected in 55.7% of patients. 46.5% of patients had an endometrial thickness of between 5- and 9.9-mm. Proliferative endometrium was the most common finding on HPE. 4.5% of cases reported endometrial malignancy. The study concluded that in peri-menopausal women with AUB, TVUS should be chosen for its convenience, accuracy and non-invasiveness. In patients with hyperplastic endometrium and/or endometrial thickness greater than 8 mm, an endometrium histopathological study is warranted to rule out atypical changes or endometrial malignancy.

Shahetal., [32] Patient age ranged from 21 to 70 years with an average age of 42.6 ± 6.9 years, with maximum patients (53.4 %) in the 41-50 years age group. The most common

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histopathological pattern was normal cyclic endometrium (47.3 %) followed by endometrial hyperplasia (42.9 %). Endometrial hyperplasia was the most common (57.1%) in the perimenopausal age group (41-50 years). The diagnostic accuracy of D &C was found to be 93.4%; amongst all histopathological patterns it was maximum for complex hyperplasia (typical and atypical) and simple atypical hyperplasia. They concluded endometrial causes of AUB are age related therefore it is specially recommended in women of perimenopausal age group to rule out preneoplastic and neoplastic aetiology. D & C is an accurate, minimally invasive outdoor procedure for detecting endometrial pathology especially hyperplasia.

Sajitha etal., [33] The results showed that AUB was the most prevalent in the perimenopausal age group. The most common complaint was menorrhagia (47%). Endometrial hyperplasia was the most common histopathological finding and was seen in 25% of patients followed by endometrial secretion in 16.7 % of patients followed by proliferative phase pattern and disordered proliferative endometrium in 12.2% of patients. Malignancy was detected in 6.4% of cases and endometrial carcinoma was the most common lesion (4.5 %). The study concluded that the histopathological assessment of endometrial samples is particularly indicated in women over 35 years of age in order to rule out malignancy and pre-neoplastic conditions. Normal physiological patterns with proliferative, secretive and menstrual changes have been observed among non-organic patients. Endometrial hyperplasia was the most common endometrial pathology in this series.

Desai etal., [34]The Abnormal Uterine Bleeding (AUB) was said to be an important symptom of both benign and serious gynaecological diseases. Abnormal perimenopausal or postmenopausal bleeding has been associated with endometrial carcinoma in approximately 10% of cases. The predominant findings of histopathological examination were proliferative endometrium at 29%, simple hyperplasia without atypia at 28%, secretion at 20 %, followed by other patterns. They concluded that the study of endometrial histopathology in perimenopausal and postmenopausal women with abnormal uterine bleeding was helpful in diagnosing endometrial hyperplasia and carcinoma.

ShobhithaG etal., [35]The most common findings were menorrhagia constituted around 40%. The endometrial thickness was 8-15mm in majority of the cases (45.50%). Endometrial hyperplasia was the commonest findings in histopathological examination of endometrium which was seen in 25 patients that comprised of 45.45%. In the study, it was mentioned that endometrial thickness of 5mm by TVS was associated with endometrial hyperplasia quoted by Bender. The study concluded thatthe efficacy of TVS with endometrial study by Dilatation and curettage in perimenopausal age group of women with AUB.The study showed that endometrial thickness cut off of >8mm.TVS is non-invasive, easily accepted by the women without any complications and further we can see the myometrium,endo-myometrialjunction, adnexa and ovaries in TVS. Thus, TVS can be tried as themost cost-effective tool as well as the initial test inwomen with abnormal uterine bleeding especially in perimenopausal age group. The maindisadvantage of TVS is technique of measuring the endometrial thickness and experience of the operator, which will affect the measurements.

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In a study conducted by **Mahapatra etal.**, [36]conclusioncame out that AUB was more commonly seen in 5th decade and in nulliparous females.Menorrhagia was the most common type of bleeding followed by metrorrhagia. Histopathological examination of the endometrium revealed that, whatever pathology may be, proliferative endometrium is the most common pattern.

Nair L etal., [37]showed that the average age for presentation was 47 years. An abnormal uterine bleeding due to menorrhagia was seen in 78.8% (52/66) of cases, poly-menorrhoea in 10.6% (7/66) of cases, polymenorrhagia in 9.1% (6/66) of cases and metrorrhagia in only one patient. 28.8% (19/66) of patients had associated dysmenorrhoea. 45.5% (30/66) of patients had associated co-morbidities. The co-morbidities were hypertensionin 40% (12/30) of cases followed by anaemia of 16.7 % (5/30). The uterus was bulky in 54.5 % (36/66) of cases and normal in size in 42.4 % (28/66) of cases as observed on USG. In 43.9% (29/66) of USG fibroid uterus cases, adenomyosis was seen in 7.6% (5/66) of cases, fibroid and adenomyosis were seen in 3% (2/66) of cases, and endometrial polyps was seen in one case. Approximately 59.1% (39/66) of patients diagnosed with USG had endometrial thicknessbetween 5-10 mm, 22 % (15/66) had thickness between 10-20 mm and 7.6 % (5/66) had endometrial thickness >20 mm, 12.1 % had endometrial hyperplasia (8/66) cases.The study concluded that transvaginal sonography is a cheap, easily available and reliable method to diagnose pathology in cases of perimenopausal bleeding. Fibroid uterus and DUB were the most common pathologies seen in the study. In the study, the rate of hysterectomy was not high and this was probably due to the fact that most patients had DUB and small fibroids and, in the absence of other endometrial pathologies, only conservative management was required. As a result, USG followed by D&C will not only increase the diagnosis of endometrial pathology, including malignancies, but will also reduce unnecessary surgical interventions such as hysterectomy. Alternatively, if hysteroscopic guided biopsy is done, the chances of missing a malignancy will still be rare.

Study was conducted by **Sedaq etal.**, [38]where the mean age (± SD) of the sample size was 47 ± 8,57 years. The average parity was 5.17 ± 2.71. The highest percentage of women in the age group was 40-59 years of age (73 %). Of the total sample size, more than half (52%) had regular cycles, 25% had irregular cycles and 23% had attended menopause. Menorrhagia was the main indication for USG in more than half of the cases followed by postmenopausal and inter-menstrual bleeding (23% and 21%, respectively). Of the 98 women (2 women were excluded from the analysis), 19% had atrophic endometrium and 67% had endometrial hyperplasia on histopathology. Transvaginal ultrasound sensitivity and specificity were 100 % and 92.9 % respectively, while transabdominal ultrasound sensitivity and specificity was 92.8 % and 65 % respectively. Thus, the study concluded that transvaginal ultrasound scanning is an excellent tool for determining whether or not further histopathological examination of endometrial biopsy is necessary for women with abnormal uterine bleeding.

CONCLUSION:

Most of the studies are concordant on age of patients presenting with AUB as >40 years with most common complaints being menorrhagia which may be because of the initiation of

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menopause causing decrease number of ovarian follicles and increased resistance to the stimulation of gonadotropin hormone that results in declining of oestrogen level. This event did not help the endometrium to grow further. Most common histopathological finding observed was proliferative endometrium which could have been due to anovulatory cycles. Exception was only present with Khan et al.,[39] who came up with endometrial hyperplasia being the most frequent finding. Sensitivity of TVUS in detecting proliferative, secretory phase and fibroid was high so it can be used as screening tool for these whereas it was found to be low in sensitivity and specificity in detecting adenomyosis, polyp, hyperplasia and carcinoma where it should be clubbed with histopathological findings for proper diagnosis, treatment and prognosis.

Hence, confirmatory diagnosis of endometrial lesions both benign and malignant is obtained by D&C, biopsy or hysterectomy which is irreplaceable by any other modality which not only helps in diagnosis, planning treatment, deciding surgery but also in prognosis of AUB. However, TVS being inexpensive and non-invasive technique can be used in addition to histopathology which only provides a rough idea of the underlying condition.
Therefore, there is need for correlating the histopathological changes with transvaginalsonography findings in patients of abnormal uterine bleeding for accurate diagnosis and management of patients of AUB.

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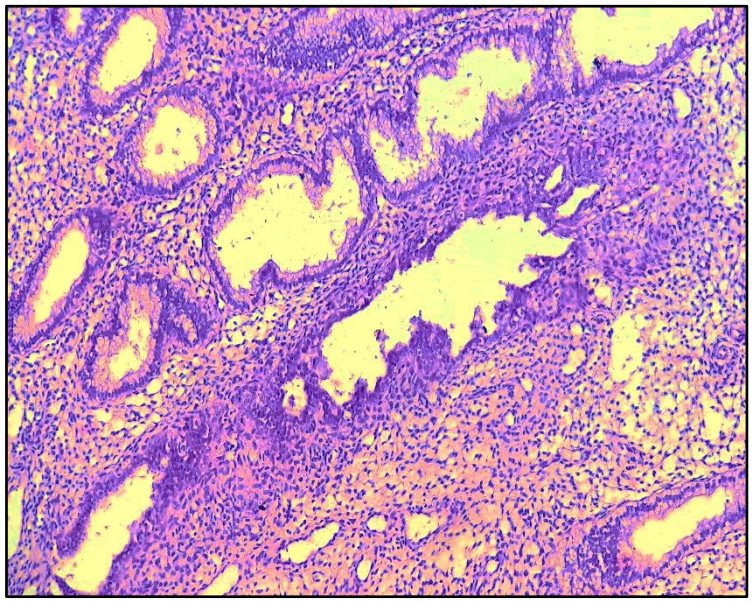

Figure 1: Section stained with routine Hematoxylin and Eosin (H& E) stain showing histopathological features of “Secretory endometrium” (Low power view: 10x).

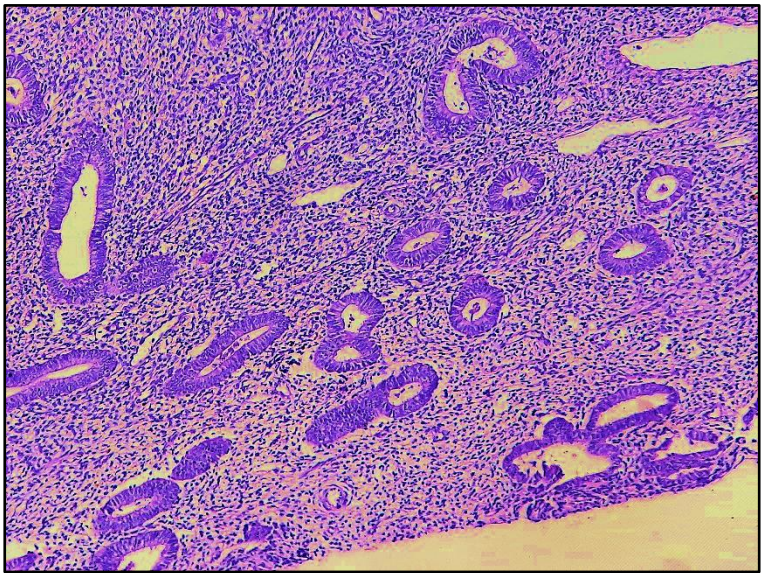

Figure 2: Section stained with routine H& E stain showing histopathological features of “Proliferative endometrium” (Low power view: 10x).

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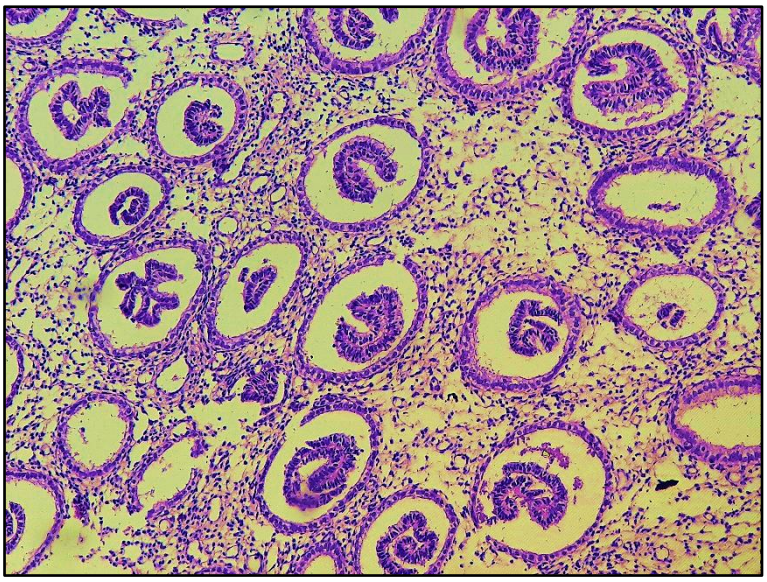

Figure 3: Section stained with routine H& E stain showing gland in gland pattern suggestive of "Hyper-oestrogenic effect" (Low power view: 10x).

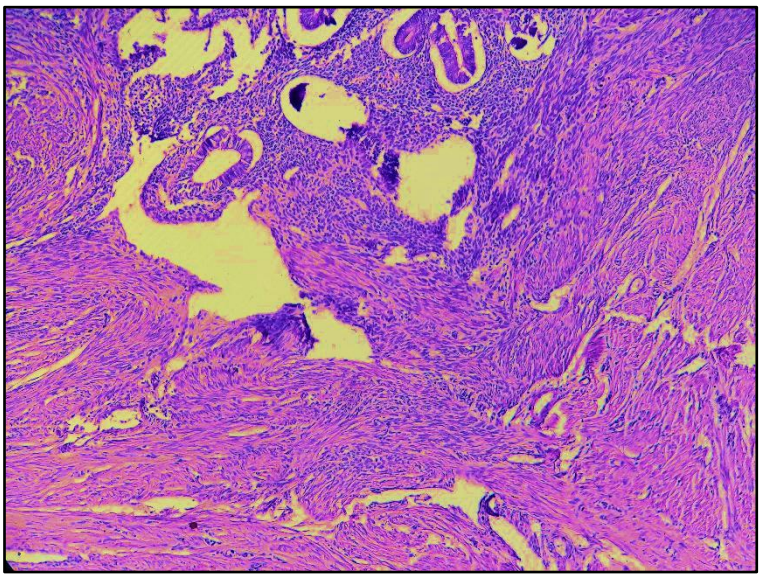

Figure 4: Section stained with routine H& E stain showing histopathological features suggestive of "Adenomyosis" (Low power view: 10x).

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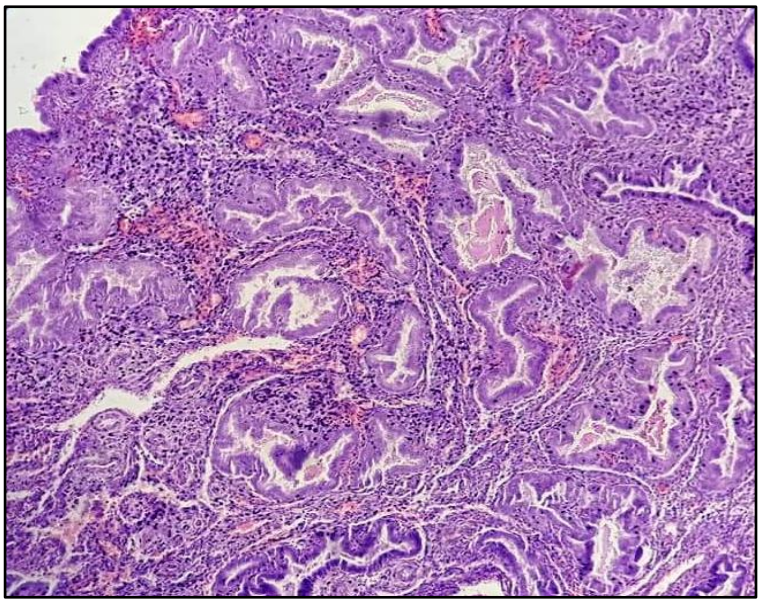

Figure 5: Section stained with routine H& E stain showing histopathological features suggestive of "Complex endometrial hyperplasia with atypia" (Low power view: 10x).

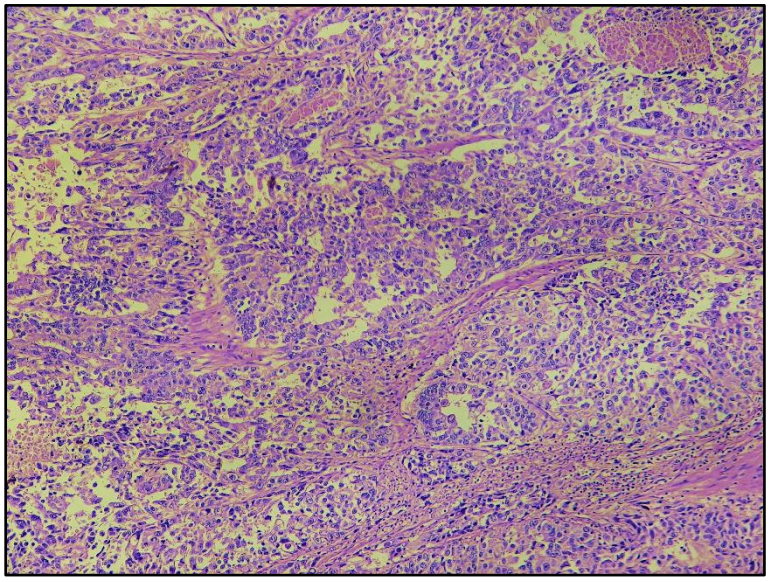

Figure 6: Section stained with routine H& E stain showing histopathological features suggestive of "Endometrial carcinoma" (Low power view: 10x).

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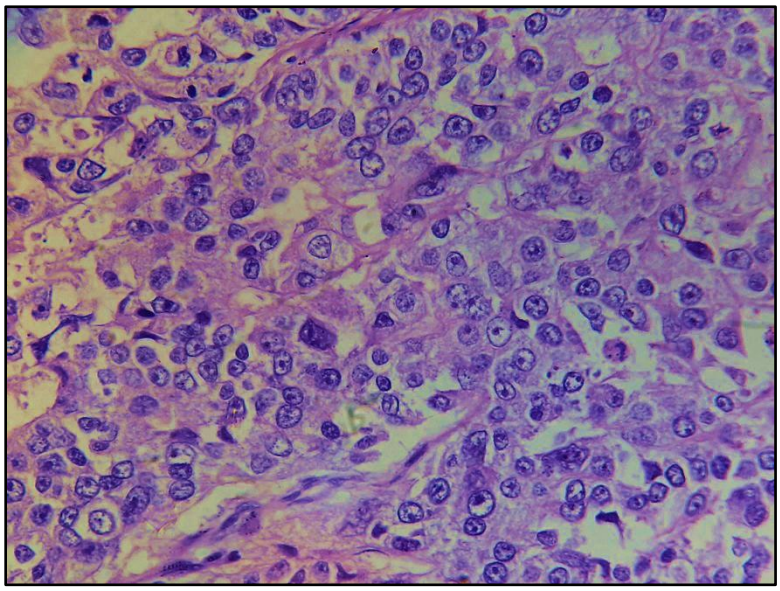

Figure 7: Section stained with routine H& E stain showing histopathological features suggestive of “Endometrial carcinoma” (High power view: 40x).