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Endometrial biopsy: Need of the hour in the management of abnormal uterine bleeding

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Abstract
Abnormal uterine bleeding refers to symptoms of excessive, scanty, prolonged, cyclic, acyclic bleeding regardless of diagnosis or cause. In SMS Medical College Jaipur, AUB accounts for approximately 20% of Gynecology OPD attendance.
In this study, we have attempted to analyze endometrial patterns in cases of AUB and to correlate the histopathology with clinical parameters and age groups.
Material and Methods: This study is a hospital based prospective study done on 214 patients of AUB attending Obstetrics & Gynaecology OPD SMS Medical College Jaipur during a period of January 2016 to March 2017. Endometrial biopsy was taken with the help of pipelle biopsy curette. Statistical analysis was done using Epi Info 7. Mean frequency was used to elaborate the data.
Results: Maximum 125 patients belonged to reproductive age group followed by 65 in perimenopausal and 24 in postmenopausal age group.
The most common pattern of bleeding was menorrhagia (52.3%) followed by menometrorrhagia (17.29%), metrorrhagia (13.08%), postmenopausal bleeding (11.21%), and premenstrual spotting (3.27%) & last was oligomenorrhoea (2.8%).
Maximum 41.1% showed secretory phase followed proliferative phase in 20% and 4.21% showed atrophic endometrium. Among abnormal findings maximum were disordered proliferative endometrium (10.28%) followed by pill endometrium (7.01%).

Keywords: Abnormal uterine bleeding, endometrial biopsy, histopathology, age group

Introduction
Abnormal uterine bleeding refers to a symptom of excessive, scanty, prolonged, cyclic, unexpected or acyclic bleeding regardless of diagnosis or cause. It is one of the most common gynecological problems that health care providers face, accounting for approximately 15-20% of office visits and 25% of gynecological operations. [1, 2] In India, women attending gynecological OPD, abnormal uterine bleeding constitute 30-50%[3]. [3] In SMS Medical College AUB cases account for approximately 20% of Gynecology OPD attendance.
Endometrial biopsy is a procedure in which a tissue sample is taken from the endometrium, and is examined under the microscope for detecting the hormonal status or any pathology.
Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first-line test. Endometrial sampling should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as seen in obesity or PCOS), failed medical management, and persistent AUB. [4] Office endometrial biopsy replaces dilation and curettage and is currently the most commonly used technique for the initial assessment of the endometrium for these women.
Management of abnormal uterine bleeding (AUB) is not complete without tissue diagnosis especially in perimenopausal and postmenopausal state as they are at higher risk for endometrial carcinoma. It is of great importance to stratify patients into high-risk and low-risk groups before therapy is initiated so that medical treatment or conservative surgery can be offered and unnecessary radical surgery can be avoided. [5, 6] In this study, we have attempted to analyze different patterns of endometrium in cases of abnormal uterine bleeding and to correlate the histopathology of endometrium with clinical parameters and age groups.

Material and Methods
This study is a hospital based prospective study done on 214 patients of abnormal uterine bleeding attending obstetrics & Gynaecology OPD of SMS Medical College during a period of January 2016 to March 2017.

Detailed clinical history was taken, physical examination and pelvic examination were done. The patients were subdivided into five groups according to the pattern of abnormal uterine bleeding i. e. menorrhagia, metrorrhagia, polymenorrhoea, menometrohagia and post-menopausal bleeding. Patients were also categorized into the following age groups: reproductive (18-45 years), Perimenopausal (>45-till menopause) and postmenopausal.

Endometrial biopsy was taken with the help of pipelle biopsy curette of those satisfying inclusion criteria

Inclusion Criteria

1. All women with abnormal uterine bleeding above 45 years of age.
2. Women with <45 years with failed medical management or unexposed estrogen exposure.
3. Women with endometrial thickness >16mm in reproductive and perimenopausal age group in phase of menstrual cycle.
4. Women with endometrial thickness >5mm in postmenopausal age group.
5. Women with postmenopausal bleeding.

Exclusion Criteria

1. Pregnancy and other related conditions
2. Blood disorders and Coagulopathy
3. Bleeding due to cervical pathology
4. Pelvic inflammatory disease
5. Intrauterine contraceptive device in situ

Histopathological examination of the endometrial biopsies was done and followed by correlation of endometrial histology with age and bleeding pattern.

Statistical Analysis

Statistical analysis was done using Epi info 7. Mean, frequency was used to elaborate the data.

Results

The present study is of 214 cases of abnormal uterine bleeding in which endometrial biopsy was done. All the biopsies were taken with pipelle endometrial biopsy curette using standard technique. [7] The cause of AUB could be determined in only 201 out of 214 endometrial biopsy as 13 biopsy samples were inadequate for evaluation.

Patients were divided into three age groups: reproductive (younger than 45 yrs), perimenopausal (45-till menopause) and postmenopausal.

Maximum 125 patients belonged to reproductive age group (58.41%) followed by 65 (30.37%) in perimenopausal age group and 24 (11.21%) in postmenopausal age group. The youngest patient was of 22 years in this series and the oldest was of 71 years of age.

The most common pattern of bleeding was menorrhagia (112 patients, 52.3%) followed by menometrorrhagia (37 cases, 17.29%), metrorrhagia (28 cases, 13.08%), postmenopausal bleeding (24 cases, 11.21%), premenstrual spotting (7 cases, 3.27%) and last was Oligomenorrhea (6 cases, 2.8%)

Different patterns of endometrium were observed on Histopathological examination. Maximum 88 samplings (41.1%) showed secretory phase followed proliferative phase in 43 biopsies (20%) and 9cases showed atrophic endometrium (4.21%).

Among endometrial findings maximum were disordered proliferative endometrium (22 cases, 10.28%) followed by pill endometrium (15 biopsies, 7.01%). Endometrial hyperplasia was classified according to W.H.O classification 1994. Simple hyperplasia without atypia was seen in 12 biopsies (5.6%) and with atypia in 3 cases (1.4%). Complex hyperplasia without atypia was observed in 2 samples (0.9%) and with atypia in 3 biopsies (1.4%).Endometrial adenocarcinoma was seen in 2 cases, both belonged to postmenopausal age group.

Endometritis was seen only in 2 cases whereas 13 samples (6.07%) could be evaluated due to insufficient tissue sample. Menorrhagia was the commonest complaint in most perimenopausal (55.93%) and reproductive age group (62.8%).

On correlating complaints with biopsy findings, maximum patients with menometrorrhagia showed secretory phase endometrium (38.8%) on Histopathological examination. Similarly in menorrhagia also, secretory phase was the commonest finding (50.4%). Proliferative phase and secretory phase were seen equally in metrorrhagia cases (36% each). Atrophic endometrium was commonest in postmenopausal bleeding (33%). All the cases of premenstrual spotting had secretory endometrium.

Discussion

Normal menstrual bleeding is defined as cyclic menstruation every 21-35 days that last fewer than 8 days with 20-80ml of blood loss [8]. Abnormal uterine bleeding can involve heavy or prolonged periods, frequent periods, intermenstrual bleeding, light periods, infrequent periods or complete absence of periods [9]. In women of child-bearing age, abnormal uterine bleeding includes any change in menstrual frequency or duration, or amount of flow, as well as bleeding between cycles [10].

Perimenopause is defined by the World Health Organization as the 2-8 years preceding menopause and the 1 year after the final menses. In postmenopausal women, abnormal uterine bleeding includes appearance of vaginal bleeding, 12 months or more after the cessation of menses, or unpredictable bleeding in postmenopausal women who have been receiving hormone therapy for 12 months or more [11].

For practical purposes, any patient who complaints of a change in her previously established menstrual pattern may be considered to have AUB.Abnormal uterine bleeding can occur due to organic causes in the uterus or due to functional disturbances related to ovulation. Various terminologies used universally for subtypes of AUB as per Speroff are-

Menorrhagia	**Bleeding occurs at normal intervals (21 to 35 days) but with heavy flow (80 mL) or duration (7 days).**
Oligomenorrhea	Bleeding occurs at intervals of > 35 days and usually is caused by a prolonged follicular phase.
Polymenorrhoea	Bleeding occurs at intervals of < 21 days
Menometrorrhagia	Bleeding occurs at irregular, noncyclical intervals and with heavy flow (80 mL) or duration (7 days).
Metrorrhagia or intermenstrual bleeding	Irregular bleeding occurs between ovulatory cycles
Postmenopausal bleeding	Bleeding recurs in a menopausal woman at least 1 year after cessation of cycles.
Dysfunctional uterine bleeding	This ovulatory or anovulatory bleeding is diagnosed after the exclusion of pregnancy or pregnancy-related disorders, medications, iatrogenic causes, obvious genital tract pathology, and systemic conditions.

Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified), known by the acronym PALM-COEIN, was introduced in 2011 by the International Federation of Gynaecology and Obstetrics (FIGO) [12].

Endometrial curettage is a routine diagnostic procedure in the evaluation of menstrual disorders.

The present study comprises of 214 cases of abnormal uterine bleeding for which endometrial biopsy was done as a diagnostic procedure attending SMS Medical College, Jaipur

Age of presentation

All patients were subdivided into three age group in a attempt to establish incidence of abnormal uterine bleeding with age. In the present study of 214 cases, maximum 58.42% cases were in reproductive age group which is concordance with the study of Shilpa and Subramanya [13]. Many studies have revealed that occurrence of menstrual disorders increases with advancing age [14, 15]. They had found maximum incidence of AUB in perimenopausal age group. Considering these discrepant observations, one may conclude that, any age after menarche is not exempt from AUB.

Pattern of bleeding in AUB

Various pattern of bleeding were studied in an attempt to establish its incidence with age. The most common complaint observed was menorrhagia (52.3%) followed by menometrorrhagia (17.29%) and metrorrhagia (13.08%) which are almost equal. The finding is consistent with the studies of Anvikar *et al* [16] and Jairajpuri *et al* [17]. These studies concluded that the most common pattern of bleeding in AUB is menorrhagia. In present study menorrhagia was the commonest complaint in reproductive age group i. e. 69.7% which is far more than any other bleeding pattern observed. Similarly in perimenopausal age group menorrhagia was the commonest complaint (55.8%) followed by metrorrhagia in 28.8%. These findings had been observed in many studies conducted previously such as those of Rajshree *et al* [18] and Muzaffar *et al* [19]

Endometrial pattern in AUB

For establishing the incidence of different endometrial patterns in AUB, this criterion had been taken up.

In the present study, most common patterns were normal cyclic physiological changes, i. e. secretory (41.12%), followed by proliferative (20.03%). This endometrial finding is consistent with the studies of Moghal [20] and Gazozai *et al* [21] the bleeding in the proliferative phase may be due to anovulatory cycles and bleeding in the secretory phase is due to ovulatory dysfunctional uterine bleeding.

However, the studies of Khan *et al* [22] and Deshmukh *et al* [23] concluded that proliferative endometrium was most common pattern, followed by secretory endometrium, followed by hyperplastic endometrium. According to the study of Singhal *et al* [24], hyperplastic endometrium was the most common pattern followed by proliferative endometrium, followed by proliferative secretory endometrium.

In the present series, disordered proliferative endometrium was seen in 10.2% cases which is quite significant number which is comparable with the study of Doraiswami *et al* [25]. Disordered proliferative endometrium is part of a continuum with endometrial hyperplasia. It resembles normal exuberant proliferative endometrium, but without uniform glandular development (some glands cystically dilated, others have shallow budding). There is increase of cystically dilated glands, but relatively normal ratio of glands to stroma. It also refers to a proliferative phase endometrium that does not seem appropriate for any one time in the menstrual cycle, but is not abnormal enough to be considered hyperplastic.

Atrophic endometrium is the most common cause of bleeding in postmenopausal stage [26]. In atrophic endometrium, thin walled veins, superficial to the expanding cystic glands make the vessel vulnerable to injury. In the present study atrophic endometrium was seen in 4.2% which is similar to study of Corneticus *et al* [26] and K. Sajitha *et al* [27].

Pill endometrium

In the present study, effect of exogenous hormone was found in 7% cases. Histological pattern of women receiving hormonal pills show combination of inactive glands, abortive secretion, decidual reaction, and thin blood vessels is characteristic. Similar incidence, i. e. 1.7%-4.81% was seen in other studies [17, 28, 29].

Endometritis

Endometritis is seldom the direct cause of AUB, but is often a contributing factor. Subepithelial capillary plexus and surface epithelium are rendered fragile by inflammatory mediators leading to breaks and micro erosions. In our study endometritis contributed to only 0.93% of abnormal uterine bleeding.

Hyperplasia

Endometrial hyperplasia is precursor for endometrial carcinoma. The classification system used by the World Health Organization (WHO) and the International Society of Gynecological Pathologists designates four different types with varying malignant potential. Based on presence or absence of architectural abnormalities such as glandular complexity and crowding, Hyperplasias are classified as simple or complex. Most important, hyperplasia are further designated as atypical if they demonstrate cytologic (i. e. nuclear) atypia. Only atypical endometrial hyperplasia are clearly associated with the subsequent development of adenocarcinoma. If left untreated, approximately 8% of patient with simple atypical hyperplasia will progress to carcinoma, whereas the progression rate in women with complex atypical hyperplasia is almost 30% in one study, and as high as 52% in another [30].

In the present study, simple hyperplasia without atypia was seen in 12 cases (5.6%) whereas with atypia was seen only in 3 cases (1.40%). Complex hyperplasia with and without atypia both was found in 3 cases (1.40%) and 2 cases (0.93%) respectively. All the cases presented with complaint of menometrorrhagia and postmenopausal bleeding.

Endometrial carcinoma

In the present study, only 2 cases of endometrial carcinoma were seen. Both cases were above 65 years of age presenting with postmenopausal bleeding. On histopathological examination, both were diagnosed as having adenocarcinoma. Out of these, one patient had vaginal metastasis as well as lung metastasis.

Unsatisfactory for evaluation

There have been very little publications about the criteria for considering an endometrial specimen as adequate or inadequate. In our study we had 13 (6%) cases of unsatisfactory samples. Most of these showed only large areas of haemorrhage and scanty glands or stroma. These were labelled unsatisfactory to report and repeat biopsy was taken.

Conclusion

Thus it can be concluded that endometrial biopsy forms one of the strongest pillar for management of abnormal uterine bleeding in all sexually active females. It gives clinician an accurate diagnosis and thus helps in deciding proper management plan. Thus it is a simple and inexpensive procedure which should be used as a first line procedure, thereby minimizing need of other costly and complicated procedures.

Table 1: Distribution of Age group

Age group	Frequency	Percent	Cum. Percent	95% CI Lower	95% CI Upper
Postmenopausal	24	11.21%	11.21%	7.32%	16.23%
Premenopausal	65	30.37%	41.59%	24.29%	37.01%
Reproductive	125	58.41%	100.00%	51.50%	65.09%
TOTAL	214	100.00%	100.00%		

Table 2: Distribution of Complaints

Complaints	Frequency	Percent	Cum. Percent	95% CI Lower	95% CI Upper
Menometrohaggia	37	17.29%	17.29%	12.48%	23.04%
Menorrhagia	112	52.34%	69.63%	45.42%	59.19%
Metrohaggia	28	13.08%	82.71%	8.87%	18.35%
Oligomenorrhoea	6	2.80%	85.51%	1.04%	6.00%
Postmenopausal bleeding	24	11.21%	96.73%	7.32%	16.23%
Premenstrual spotting	7	3.27%	100.00%	1.33%	6.62%
TOTAL	214	100.00%	100.00%		

Table 3: Distribution of Biopsy Findings

Biopsy findings	Frequency	Percent	Cum. Percent	95% CI Lower	95% CI Upper
Atrophic endometrium	9	4.21%	4.21%	1.94%	7.83%
Complex hyperplasia with atypia	3	1.40%	5.61%	0.29%	4.04%
Complex hyperplasia without atypia	2	0.93%	6.54%	0.11%	3.34%
Disordered proliferative endometrium	22	10.28%	16.82%	6.56%	15.15%
Endometrial carcinoma	2	0.93%	17.76%	0.11%	3.34%
Endometritis	2	0.93%	18.69%	0.11%	3.34%
Inadequate tissue	13	6.07%	24.77%	3.27%	10.16%
Pill endometrium	15	7.01%	31.78%	3.98%	11.30%
Proliferative phase	43	20.09%	51.87%	14.94%	26.10%
Secretory phase	88	41.12%	92.99%	34.46%	48.03%
Simple hyperplasia with atypia	3	1.40%	94.39%	0.29%	4.04%
Simple hyperplasia without atypia	12	5.61%	100.00%	2.93%	9.59%
TOTAL	214	100.00%	100.00%		

Table 4: Age group wise distribution of complaints

Age group	Meno metrorrhagia	Menorrhagia	Metrorr hagia	Oligomenorrhea	Post-menopausal bleeding	Premenstrual spotting	Total
Postmenopausal	0	0	0	0	21	0	21
Premenopausal	17	33	8	0	0	1	59
Reproductive	19	76	17	4	0	5	121
TOTAL	36	109	25	4	21	6	201

Table 5: Biopsy finding in different complaints

Complaints	Atrophic endometrium	Complex hyperplasia with atypia	Complex hyperplasia without atypia	Disordered proliferative	Endometrial carcinoma	Endometritis	Pill endometrium	Proliferative phase	Secretory phase	Simple hyperplasia with atypia	Simple hyperplasia without atypia	Total
Menometrorrhagia	2	0	1	5	0	1	3	6	14	1	3	36
Menorrhagia	0	2	0	12	0	1	9	24	55	0	6	109
Metrorrhagia	0	0	0	2	0	0	3	9	9	0	2	25
Oligomenorrhea	0	0	0	0	0	0	0	1	3	0	0	4
postmenopausal bleeding	7	1	1	3	2	0	0	3	1	2	1	21
premenstrual spotting	0	0	0	0	0	0	0	0	6	0	0	6
TOTAL	9	3	2	22	2	2	15	43	88	3	12	201

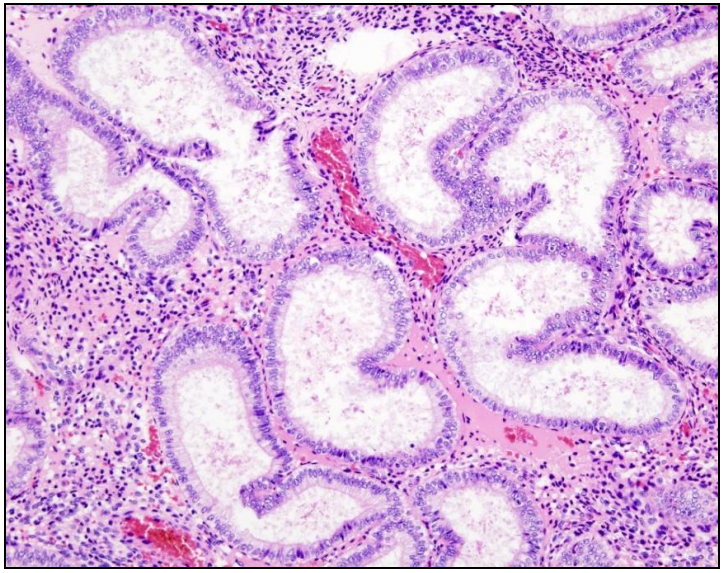

Fig 1: Secretory Endometrium

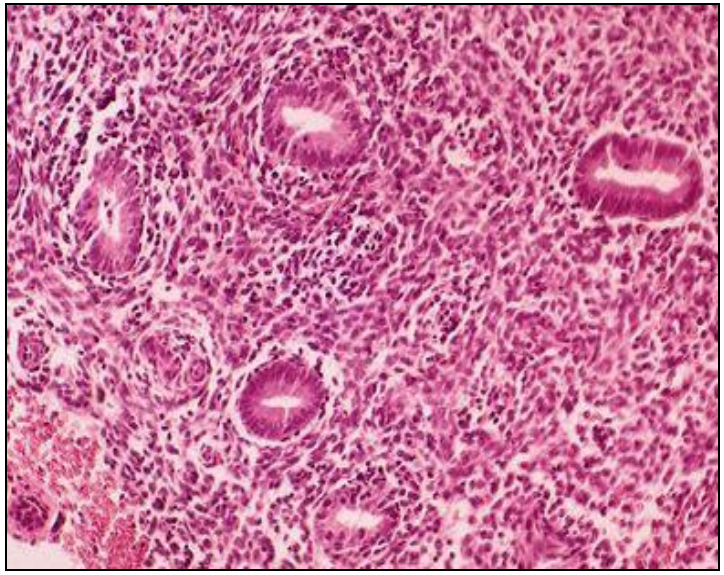

Fig 2: Proliferative endometrium

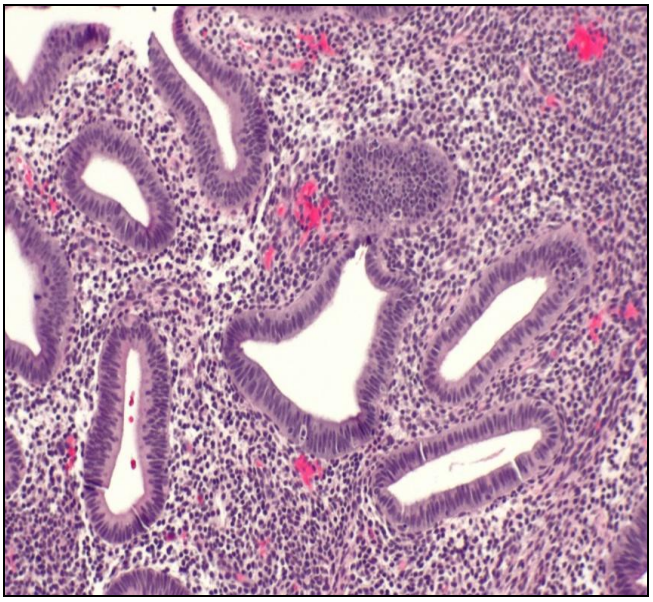

Fig 3: Disordred proliferative endometrium

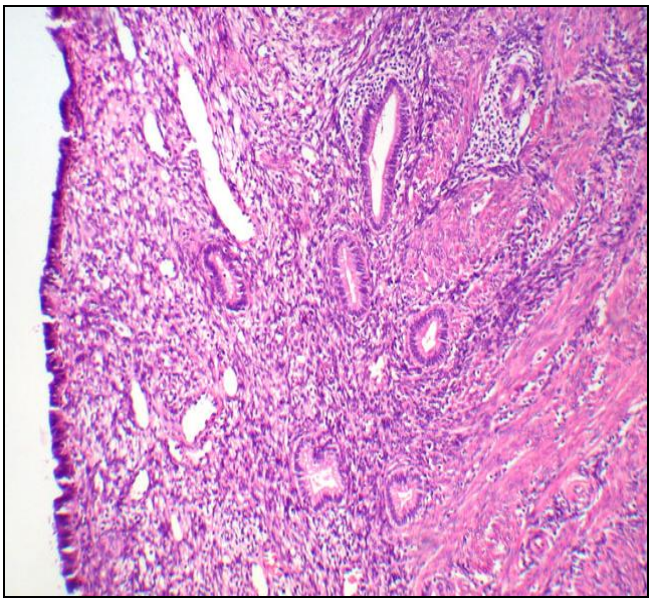

Fig 4: Atrophic endometrium

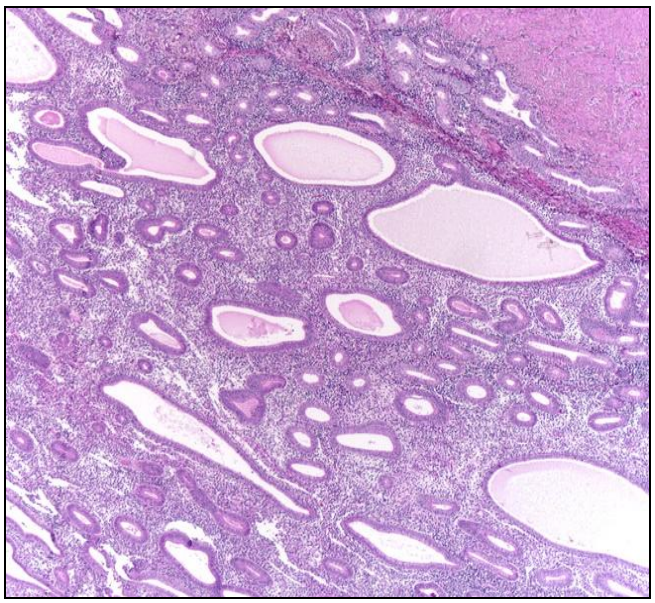

Fig 5: Simple hyperplasia without atypia

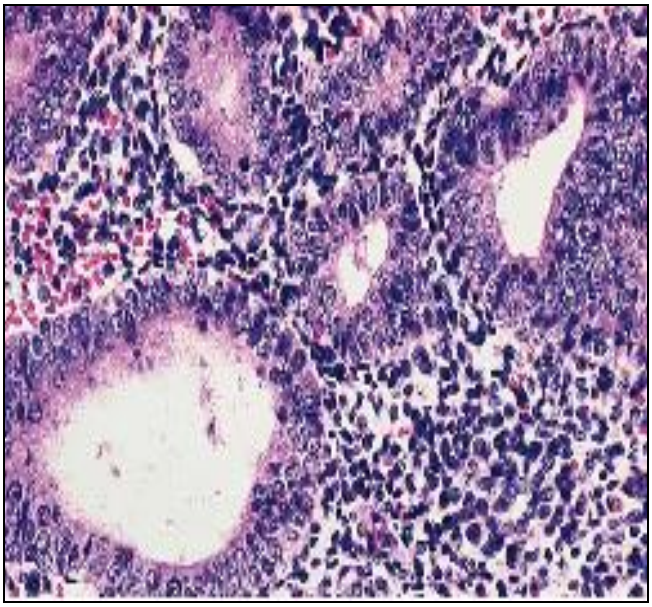

Fig 6: Simple with atypia

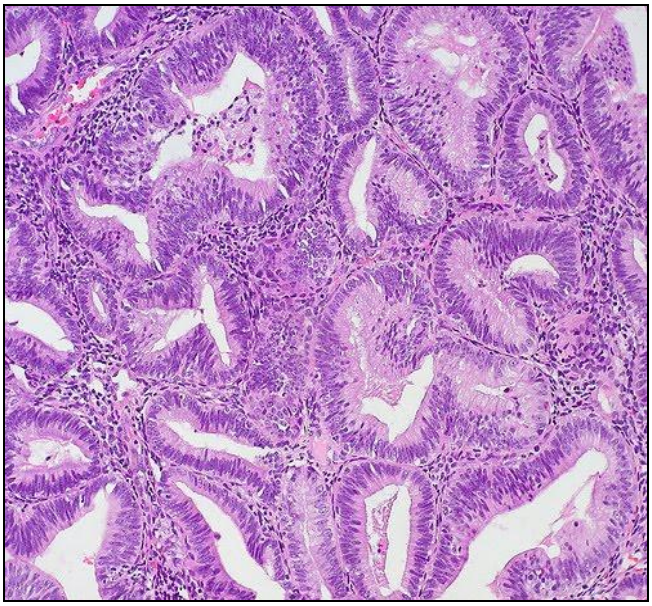

Fig 7: Complex hyperplasia without atypia

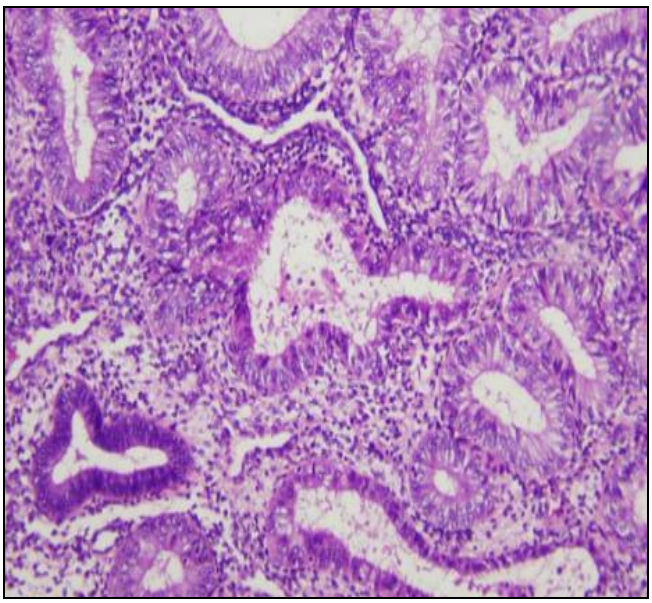

Fig 8: Complex hyperplasia wihatypia

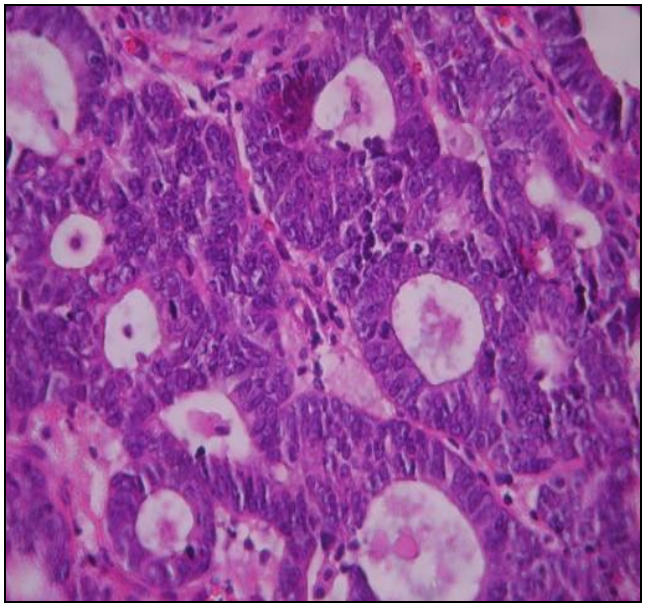

Fig 9: Endometrial cancer (Adenocarcinoma)

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