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Study of Morphological Patterns of Endometrial Curettings in Dysfunctional Uterine Bleeding: A Study of 161 Cases, with Review of Literature

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Abstract

Dysfunctional uterine bleeding is irregular uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. Endometrial biopsy is often the first diagnostic tool in a case of dysfunctional uterine bleeding. A total of 161 cases were analysed during a period of two years, from January 2015 to January 2017 in the Department of Pathology, BGS Global Institute of Medical Sciences. The frequency of the various endometrial patterns with comparison of the patterns in different age groups was observed and documented.

Keywords: Dysfunctional Uterine Bleeding; Endometrium; Dilatation and Curettage.

Introduction

Endometrial biopsies form a major proportion of workload to the pathologists. Adequacy of endometrial samples is often compromised by the presence of artifacts, fragments from other sites and advent of newer methods of performing biopsies which yield scant material; thus resulting in challenges associated with reporting. Obtaining optimal diagnostic result is largely dependent on when in the menstrual cycle is the curettage performed. The clinician should ensure that the time of curettage is mentioned along with the suspected clinical diagnosis of the underlying pathology. Many a times patients undergoing a curettage are already taking exogenous hormones; thus, pathologists need to be well versed with endometrial changes associated with hormone intake. Endometrial biopsy is often the first diagnostic tool in a case of dysfunctional uterine bleeding because it is much more inexpensive compared to than hormonal assays and has often been proved as an effective therapeutic tool. This study was done to analyse all the endometrial samples received in the Department and the frequency of the various endometrial patterns with the comparison of the patterns in different age groups.

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Materials and Methods

This study was undertaken for a period of two years, from January 2015 to January 2017 in the Department of Pathology, BGS Global Institute of Medical Sciences. Relevant clinical data were collected for all cases.

Inclusion Criteria

1. Dysfunctional uterine bleeding

Exclusion Criteria

1. Organic lesions such as leiomyoma, adenomyosis.
2. Pregnancy related complication presenting with abnormal bleeding
3. Hysterectomy specimens.

Timing for Biopsy

In order to get optimal result, timing of biopsy is very crucial. In infertility patients- The differential diagnosis of the various causes of infertility is best made shortly before the onset of menstruation. In menorrhagia due to irregular shedding, best time for

curettage is from 5 to 10 days on menstruation, in order to recognise remnants of non lysed mucosa. In metrorrhagia, curettage is best done without delay when much of endometrium is available for examination. With amenorrhea in a patient in reproductive age group, a pregnancy must be excluded before curettage is performed.

Technique

Specimens were fixed in 10% Neutral buffered formalin, processed and embedded in Paraffin.

3-4 μ thick sections were made, stained with Hematoxylin and eosin. A total of 161 cases were analysed and histological diagnosis was made. Microscopic examination was done by 3 pathologists independently to reduce observer bias.

Results

A total of 161 samples with a clinical diagnosis of abnormal uterine bleeding were studied. Patient's age ranged from 25 years to 72 years. Most of the patients were seen in the age group of 40-49 years [Chart 1].

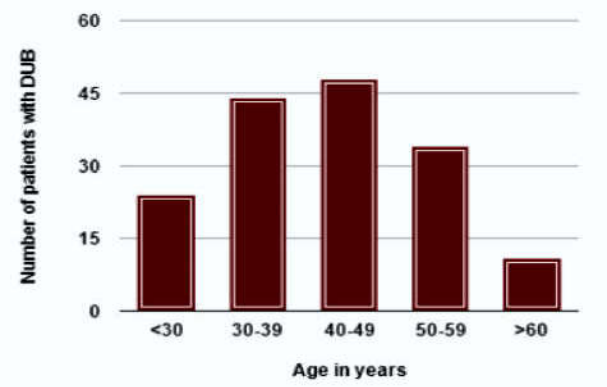

Chart 1: Distribution of cases in various age groups

The most common pathology observed in the study was endometrial hyperplasia. It was seen in 41 cases (21.4%) followed by Disordered Proliferation in 22 cases (13.6%) [Table 1].

Endometrial hyperplasias has been traditionally classified based on the four tier system of classification [Chart 2]. However in the latest classification published in 2014, WHO has come up with a two tier system of classification. Table 2 shows our cases of endometrial hyperplasia according to the latest WHO classification- 2014.

Table 1: Distribution of endometrial patterns

Endometrial Patterns	No of Cases
Proliferative phase	18
Secretory phase	19
Disordered proliferative phase	22
Decidual reaction	8
Menstrual pattern	2
Irregular shedding	11
Deficient secretory	2
Deficient proliferation	2
Irregular proliferation	4
Non secretory	1
Endometritis	1
Dysmenorrhea membranacea	1
Basal proliferation	2
Endometrial polyp	10
Endometrial hyperplasias	41
Cystic hyperplasia	2
Endometrial carcinoma	3
Inadequate	12
Total	**161**

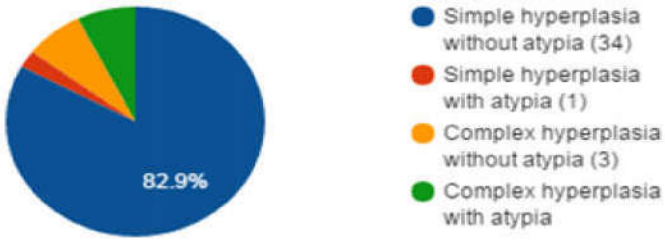

Chart 2: Number of cases of endometrial hyperplasias (41 cases)

Table 2: Number of cases of Endometrial hyperplasia*

Endometrial Hyperplasia*	No of Cases
Hyperplasia without atypia	37
Atypical hyperplasia/ Endometrioid intraepithelial neoplasia	4
Total	41

* According to the new WHO classification of Endometrial hyperplasia 2015.

Endometrial carcinoma was seen in 3 cases (1.8%). All the three patients were above 50 years of age [Table 3]. 12 biopsies were reported to be inadequate [Table 3], of which rebiopsy was done only in 5 cases.

Table 3: Endometrium in Different age groups

Endometrial Pattern	<30 years	30-39	40-49	50-59	>60 years	Grand Total
Proliferative phase	0	5	6	5	2	**18**
Secretory phase	3	10	6	0	0	**19**
Disordered proliferative phase	6	1	6	7	2	**22**
Decidual reaction	4	1	2	1	0	**8**
Menstrual pattern	0	1	1	0	0	**2**
Irregular shedding	2	1	4	4	0	**11**
Deficient secretory	0	2	0	0	0	**2**
Deficient proliferation	0	2	0	0	0	**2**
Irregular proliferation	0	2	2	0	0	**4**
Non secretory	0	0	0	0	1	**1**
Endometritis	0	1	0	0	0	**1**
Dysmenorrhea membranacea	0	1	0	0	0	**1**
Basal proliferation	0	1	1	0	0	**2**
Endometrial polyp	1	1	4	4	0	**10**
Endometrial hyperplasias	6	10	14	9	2	**41**
Cystic hyperplasia	0	0	0	2	0	**2**
Endometrial carcinoma	0	0	0	1	2	**3**
Inadequate	2	5	2	1	2	**12**
Total	**24**	**44**	**48**	**34**	**11**	**161**

Discussion

Abnormal uterine bleeding has been used to describe any bleeding not fulfilling the criteria for normal menstrual bleeding. The causes of abnormal uterine bleeding include a wide spectrum of diseases of the reproductive system and non-gynecologic causes as well. Organic cause of abnormal uterine bleeding may be subdivided into reproductive tract disease, iatrogenic causes and systemic disease. When an organic cause of AUB cannot be found, then by exclusion, a diagnosis of dysfunctional uterine bleeding is assumed [1]. The diagnoses encompassed within Dysfunctional uterine bleeding can be classified under three definable headings: (1) disorders of endometrial origin (disturbances of the molecular mechanisms responsible for regulation of the volume of blood lost at menstruation); (2) disorders of the hypothalamic-pituitary-ovarian axis; and (3) disorders of hemostasis (the ''coagulopathies''). These three groups of diagnoses are sometimes referred to as ''non structural'' causes of abnormal uterine bleeding [2].

In the reproductive years, the endometrium is characterized by cyclical growth, shedding, and regrowth in response to estrogen and progesterone secretion by the ovaries. Endometrial morphology, as a consequence, is continually altering depending on the levels of estrogen and progesterone [3]. Disease states of varying intensities that superimpose themselves on these fluctuating functional changes often produce complex admixtures of functional state and the damage wrought by the pathologic processes. Accordingly pathologists have to be well versed with various functional and pathological changes in endometrium and the functional and morphological diagnosis has to represent the result of close

cooperation of attending gynecologist [4]. Endometrial biopsies have proved to be an effective diagnostic modality with sensitivity for the detection of endometrial abnormalities being as high as 96% [5]. Pathologists often receive scant tissue, making it difficult for interpretation. However, caution should be exercised before categorizing an endometrial biopsy as inadequate or insufficient because this can have management and medicolegal implications. It should be kept in mind that in majority of cases, the presence of only scant tissue in an endometrial specimen is not a reason for a repeat biopsy, provided the endometrial cavity has been entered, and at least some endometrial tissue is present in the biopsy specimen to confirm this. It has been suggested that with an endometrial biopsy containing scant tissue that cannot be typed, the term unassessable is more appropriate than inadequate or insufficient. In such cases, the gynecologist should correlate the biopsy results with the ultrasonic and/or hysteroscopic findings. If there is a clinical suspicion of hyperplasia or malignancy, for example, if there is recurrent postmenopausal bleeding, or if the ultrasonic and/or hysteroscopic findings are worrying, then Dilatation and Curettage should be performed. If the above investigations suggest an atrophic endometrium, rebiopsy is probably unnecessary [3].

An important problem faced by pathologists is dealing with artifacts in endometrial biopsies. There are several common artifacts in endometrial biopsy specimens that occasionally may be misinterpreted as an endometrial hyperplasia or even a carcinoma. Telescoping is common and refers to the presence of glands within glands. Artifactual crowding and compression of glands are also common and may result in consideration of a complex endometrial hyperplasia. An artifact that is especially common with, but not exclusive to outpatient biopsies is the presence of superficial strips of endometrial epithelium, sometimes accompanied by a little stroma, with a pseudopapillary architecture. This may result in consideration of a wide range of papillary lesions, benign and malignant, which occur in the endometrium. Such superficial strips of pseudopapillary epithelium, which are generally atrophic, should be examined carefully under high power to look for proliferative activity and nuclear atypia. Crushed endometrial glands and stroma may be extremely cellular and can cause concern. Extensive crush artifact is more likely to occur in biopsies from atrophic endometrium in postmenopausal patients. As with the examination of other tissues, crushed elements should not be viewed in isolation. Another artifact secondary to cautery is vacuolation of the endometrial stromal cells, resulting in a signet-ring appearance. Squamous metaplasia is one of the commonest forms of endometrial epithelial metaplasia. Although usually a focal finding, on occasions there may be widespread squamous metaplasia with obliteration of the glandular lumina such that it is difficult to assess the underlying glandular component. This is especially common when the squamous metaplasia is of the morular type. Squamous metaplasia is common in endometrioid adenocarcinoma and in endometrial hyperplasias and polyps; these should be excluded by careful examination of the glandular elements. (Fig 1) [3].

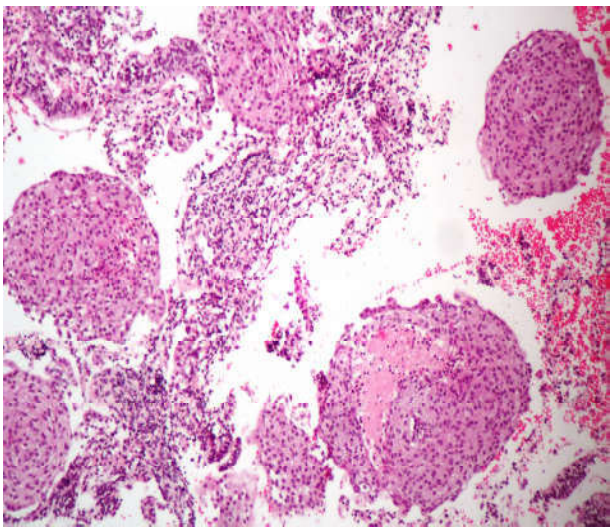

Fig. 1: Squamous metaplasia (morular type)

The most common age group presenting with excessive bleeding in our study was 40-49 years. A similar incidence has been reported by Yusuf et al. and Muzaffar et al. in their study of endometrium [6,7]. The reason for increased incidence of dysfunctional uterine bleeding in 40 years age group may be due to the fact that these patients are in their climacteric period. As women approach menopause, cycles shorten and often become intermittently anovulatory due to a decline in the number of ovarian follicles and the estradiol level. 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 [8]. Predominant number of cases (25%) in our study showed normal physiologic phases such as proliferative, secretory, menstrual and atrophic pattern.

Deficient proliferation is seen in deficient follicular stimulation causing an anovulatory cycle or due to iatrogenic suppression by hormone therapy. It is morphologically composed of small glandular and stromal elements when compared with the normal

proliferative phase. In irregular proliferation the growth of glands and stroma exceeds that of normal proliferation. The glands are irregular in shape, lining epithelium is pseudostratified and forms a dense row with many mitosis. The stroma is densely cellular and focally edematous. Irregular proliferation is a transition form to glandular cystic hyperplasia and is often due to excessive estrogen production [4]. There were 2 cases of deficient proliferation and 4 cases of irregular proliferation in our study.

In irregular shedding, the corpus luteum develops normally but fails to regress at the proper time and continue to secrete progesterone until this secretion subsides slowly and gradually. Consequently, endometrial regression is protracted and irregular shedding is prolonged and irregular. Distinction is of clinical significance between irregular shedding due to hyperstimulation by placental remnants and that unassociated with previous pregnancy. A positive Arias stella reaction is indicative of a recent intra or extra uterine abortion. The presence of endometritis and hyalinised arterioles may help differentiate intra from extra uterine cause pregnancy. However necrotic debri in the endometrium may be found in any cause for irregular shedding.

Pill endometrium (Decidual reaction) shows a combination of inactive glands, abortive secretions, decidual reaction and thin blood vessels. This pattern may be associated with previous pregnancy or in patients in perimenopausal women resorting to hormonal treatment for bleeding. We had 8 cases of decidual reaction in our study.

There was one case of Dysmenorrhea membranacea in our study (Fig. 2). The morphological substrate for this clinical diagnosis is the finding of large sheet like pieces of more or less well preserved predecidual or decidual endometrium which has been shed undissociated from the uterine cavity. The plane of separation is clearly recognised by the zone of hemorrhagic necrosis. This generally follows an abortion or persistent corpus luteum unassociated with pregnancy. Distinction between the above two causes of dysmenorrhea membranacea is difficult in the absence of placental remnants and Arias Stella reaction, but may be possible when the endometrial glands are non convoluted, narrow and lined by atrophic epithelium; such an arrested secretion is seen only after gestagen therapy [4].

Endometritis was seen in 12 cases in our study in association with other dominant endometrial pathology (not represented in table). Endometritis is often presents with DUB, pelvic pain and infertility, therefore it needs to be diagnosed, because with specific treatment endometrium starts functioning normally.

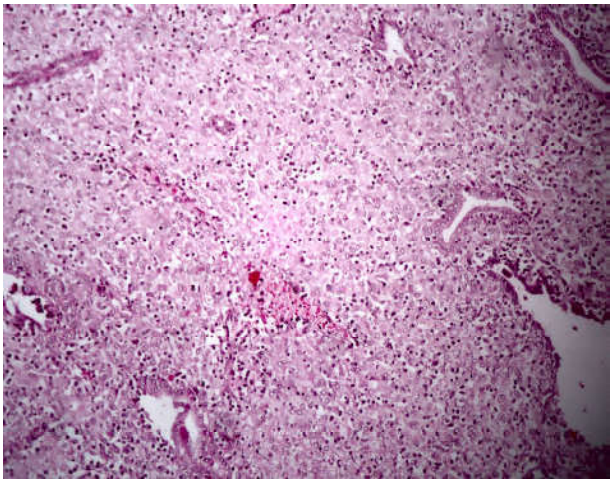

Fig. 2: Dysmenorrhea membranacea

Disordered proliferative pattern lies at one end of the spectrum of proliferative lesions of endometrium that includes carcinoma at the other end, with intervening stages of hyperplasias. The term "disordered proliferative endometrium" has been used in a number of ways and is somewhat difficult to define. It denotes an endometrial appearance that is hyperplastic but without an increase in endometrial volume. 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. Disordered proliferative pattern resembles a simple hyperplasia, but the process is focal rather than diffuse [9]. Disordered proliferation was seen in 13 % of the cases in our study (table 1).

Endometrial polyps develop from focal hyperplasias. At first a polyp has a broad base. When the surrounding is repeatedly shed with menstruation, the base of the polyp becomes a slim stalk (Fig 3) [4]. Accurate typing of the endometrium is, in general, not possible when polyps, endometritis, or other pathological lesions are present, and therefore not attempted. Our cases of endometrial polyps were predominantly in 40-49 years age group. Lower incidence of polyps in younger age group may be attributed to a possible spontaneous regression mechanism, which is characteristic of cyclic endometrium in reproductive age group [10].

Endometrial hyperplasia was seen in 25% of the cases, most commonly between 40-49 years. A lot of importance has gone into classifying endometrial hyperplasias to recognise those that are precursors to

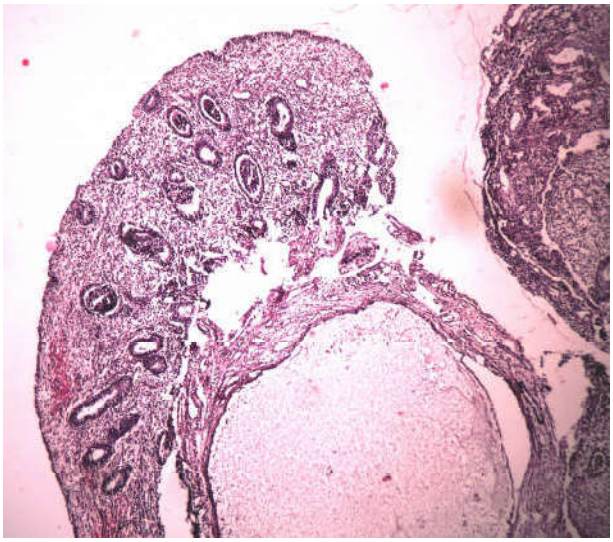

Fig. 3: Endometrial glandular polyp

carcinoma. The underlying cause of these hyperplasias is a relative predominance of estrogen combined with insufficient progesterone levels. Typical causes include corpus luteum insufficiency/anovulatory cycles (premenopause), polycystic ovary syndrome and obesity with metabolic syndrome, inappropriate hormone therapy post menopause (insufficient dosage of gestagens) or an estrogen or androgen-producing tumor [11].

Up to now, the correct clinical evaluation of endometrial hyperplasias was made more difficult by the different classification systems still in use: In 1994, the WHO classified endometrial hyperplasias into 4 categories:

1. Simple hyperplasia without atypia
2. Complex hyperplasia without atypia
3. Simple atypical hyperplasia
4. Complex atypical hyperplasia [12].

The WHO classification of 1994 and even more so the parallel use of the older classification system led to confusion among clinicians.

The consequence of this was inadequate diagnosis, with hysterectomies performed for hyperplasias without atypia or gestagens administered in hormone replacement therapy dosages for atypical hyperplasia. Pathologists also experienced difficulties with categorization [11]. In its latest classification published in 2014, the WHO has clarified the matter: it now only differentiates between 2 categories of endometrial hyperplasia:

1. Hyperplasia without atypia (Figure 4)
2. Atypical hyperplasia/endometrioid intraepithelial neoplasia [14] (Figure 5)

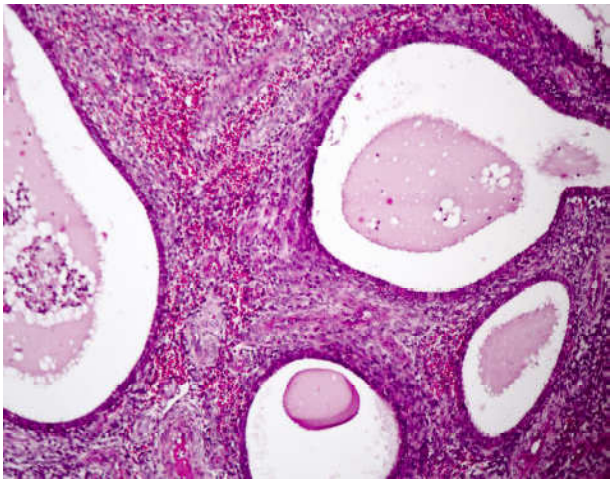

Fig. 4: Hyperplasia without atypia

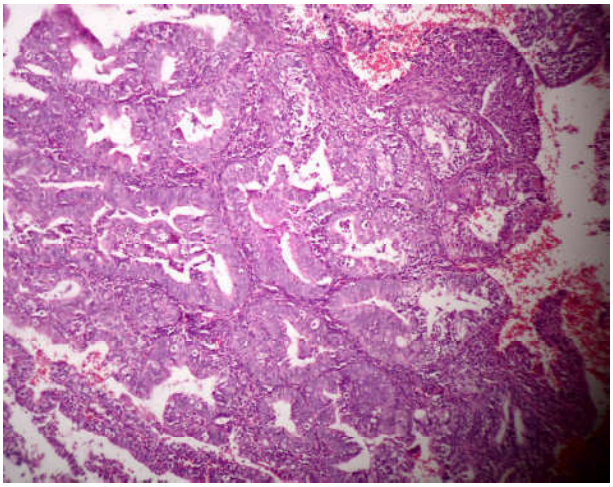

Fig. 5: Atypical hyperplasia/ endometroid intraepithelial neoplasia

This reduction to 2 categories was not only due to the need to do away with the confusing multitude of terms currently in use. Rather, it reflects a new understanding of molecular genetic changes. Hyperplasias without atypia exhibit no relevant genetic changes. They are benign changes and will regress again after the endocrine milieu (physiological gestagen levels) has normalized. In a few cases (1–3 %), progression to invasive disease may occur if the endocrine disorder (long-term estrogen dominance or relative or absolute gestagen deficiency) persists over the long term. Atypical endometrial hyperplasias exhibit many of the mutations typical for invasive endometrioid endometrial cancer [11]. In up to 60 % of cases, patients have coexisting invasive cancer or are at extremely high risk of developing invasive cancer. The implications for treatment are obvious: hyperplasias without atypia should generally be treated conservatively (normalization of the cycle through weight loss, metformin; oral contraceptives;

cyclical gestagens; gestagen IUD). Preventive hysterectomy should only be considered in exceptional cases (e.g., extreme obesity without any prospect of weight loss). Treatment of atypical hyperplasia/ endometrioid intraepithelial neoplasia should generally consist of total (not supracervical) hysterectomy. Conservative treatment with high-dose gestagens and close histological monitoring should only be considered in exceptional cases (when the patient wants to have children, satisfactory compliance) [11,13].

There were 3 cases of Endometrial carcinomas in this study. There was one case of Malignant mixed mullerian tumor (Figure 6) and three case of Endometrioid carcinoma, (Figure 7) one with extensive squamous differentiation.

There were two cases of cystic hyperplasia in our study both in the age group of 50-59 years. The exact cause of bleeding in patients more than 50 years cannot be postulated, but it may be due to anatomic vascular variations or local abnormal haemostatic mechanisms. Thin walled veins, superficial to the expanding cystic glands make the vessel vulnerable to injury [8].

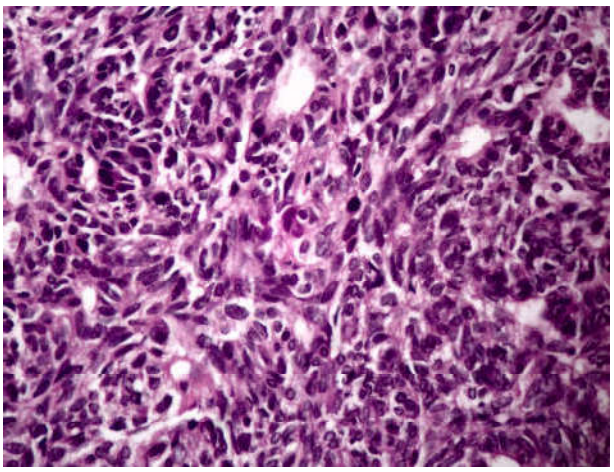

Fig. 6: Malignant mixed mullerian tumor

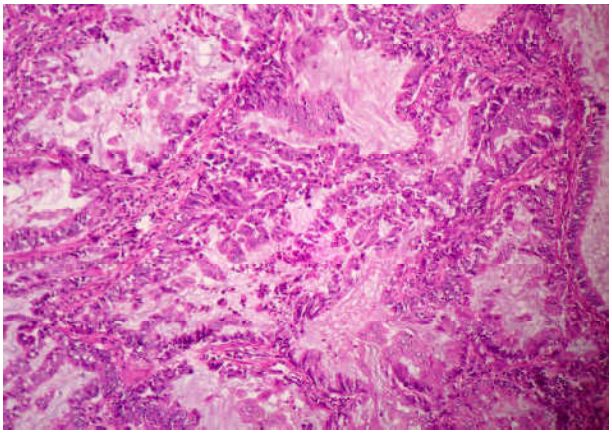

Fig. 7: Endometrioid carcinoma

Conclusion

Etiology of abnormal uterine bleeding varies with age. Dilatation and curettage is useful for diagnosis, to plan management modality and to assess therapeutic response [8]. Since neoplastic processes are more common in perimenopausal and post menopausal age group, endometrial biopsies are indicated in woman above 40 years to rule out malignancies.

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