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Original Article

Spectrum of Histological Changes in Endometrial Biopsies with Abnormal Uterine Bleeding

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Abstract

Objective: To identify and characterize the diagnostic features of endometrial biopsies in cases presenting with abnormal uterine bleeding and to determine the types and frequencies of endometrial pathologies in these cases.

Materials and Methods: The study was conducted at Department of Pathology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. The duration of study was 6 months. The study included 100 cases of endometrial biopsies. Relevant clinical history was taken from the patient and the results of other investigations were also noted. The specimens were grossed and then processed. Cutting of sections was done at 3 to 5 microns, and stained with H&E. Slides were evaluated for positive histopathological findings.

Results: Most of the patients were in the age of 20 to 50 years with mean age of 37 years.

The various conditions responsible for abnormal uterine bleeding in this study were 34 cases of estrogen dominance, 10 cases of abnormal secretory phase, 6 cases of anovulatory endometrium, 6 cases of pill-effect endometrium, 3 cases of simple cystic hyperplasia, 3 cases of chronic endometritis, 2 cases of luteal phase defect and 1 case of atrophic endometrium. All these patients were in the age group 20 to 60 years and most of the samples were in the age group 30 to 45 years. Polymenorrhagea was the most common complaint. The results of this study are compared with national and international studies.

Conclusion: Hormonal imbalance is a very broad term and may lead to misinterpretation. It will be a challenge for the pathologists to do serum hormone levels for each and every patient and to correlate it with histopathological findings.

Complete clinical history is very important in this regard especially LMP and hormonal therapy has a crucial role in the diagnosis of endometrial biopsies.

Keywords: Endometrium, estrogen dominance, abnormal secretory phase endometrium.

Introduction

Endometrial biopsies are amongst the commonest specimens received for histopathological interpretation which are commonly encountered in the surgical pathology laboratory. Such specimens are taken from the women aging 20 to 60 years for a variety of reasons and then the histopathological examination is required to consider a wide range of

Contribution of Authors: Dr. Purdil study designed, collected the samples, reviewed the slides with staff pathologist and wrote initial manuscript. Dr. Farhan reviewed the manuscript and helped with references. Dr. Ahmareen was involved in reviewing all the biopsy slides, planning, compiling and analyzing data.

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benign and malignant conditions.

The current study emphasizes on the morphological appearance of endometrial biopsies in common conditions which mainly present with abnormal uterine bleeding, such as abnormal hormonal status, endometeritis, polyps, dysfunctional uterine bleeding, infertility, fibroids, spectrum of hyperplasia and endometrial cancer. Dysfunctional uterine bleeding is a diagnosis of exclusion, and therefore no organic lesion e.g. fibroid or polyps etc. should be present before rendering the diagnosis of dysfunctional uterine bleeding.

Dysfunctional uterine bleeding is most common near the beginning and end of a woman's reproductive life but may occur at any time[1]. In the first 18 months after menarche, the immature hypothalamic-pituitary axis may fail to respond to estrogen & progesterone resulting in anovulation[1]. In the obese women the non-ovarian endogenous estrogen production may upset the normal menstrual cycle[2]. As menopause approaches, decrease in hormone levels or irresponsiveness to hormone may also lead to anovulatory dysfunctional uterine bleeding.

In addition, a luteal phase defect as well as improper balance of estrogen and progesterone may result in dysfunctional uterine bleeding[3].

The importance of clinical history; particularly menstrual history, hormonal therapy and past obstetric history cannot be overemphasized. The endometrial curetting biopsy must be interpreted in systemic fashion keeping history and physical findings in mind. Endometrial tissue is taken in a very simple and easy way. It can be done in a doctor's office or in an operating theatre. No anesthesia or hospitalization is needed. During this procedure, a small amount of the endometrium from the uterine cavity is curetted and sent for histopathological examination. This is a procedure done just before the menstrual cycle starts[4]. It provides an adequate sample for diagnosis of endometrial diseases in 90% to 100% of cases. This is the most commonly used diagnostic test for various abnormal endometrial conditions.

Methodology

The endometrial curetting were received in 10% formal saline, and labelled for patient name, gender, age and then specimens were given specific ID number. The gross descriptive details i.e. measurements, weight and color were noted. After tissue processing the slides were stained with Hematoxylin and eosin.

Inclusion Criteria: All the endometrial biopsies sent for histopathological evaluation to the Pathology Department with history of abnormal uterine bleeding were included in the study.

Exclusion Criteria: Biopsies without adequate clinical history was not available were excluded from the study

Data Collection Procedure:

- All the relevant information regarding the age, menstrual cycle, ultrasonographic findings and date of procedure were presented in patient proforma sheet.
- All the microscopic findings of the endometrial biopsies were included in histopathological evaluation proforma. The histopathological evaluation proforma included all the information regarding status of the glands, the lining cells, location of nuclei and status of stroma showing edema, spindly nature, presence or absence of plasma cells, eosinophilic syncytial change and status of the blood vessels i.e. thin walled venules, thickened arterioles.

Data Analysis: All data was entered into SPSS version 17. Frequencies of various pathologies like hormonal imbalance, endometritis, abnormal secretory phase, anovulatory endometrium etc. were calculated.

Results

One hundred cases of endometrial curettings were collected over a period of 6 months, from February 2010 to August 2010 at Pakistan Institute of Medical Sciences Islamabad. Specimens were received as multiple soft tissue fragments, ranging in weight from 0.4 grams to 2.5 grams. All these women had a history

of abnormal uterine bleeding, the detail is shown in Figure 1. Ultrasonographic findings were available in all the 100 patients, however only 31 patients were showing abnormal findings. (Figure 2)

Among 100 cases the most common pattern was estrogen dominance accounting for 34 cases, characterized by spindly stroma, proliferative lining epithelium of the glands and clusters of thick walled blood vessels. (Figure 3)

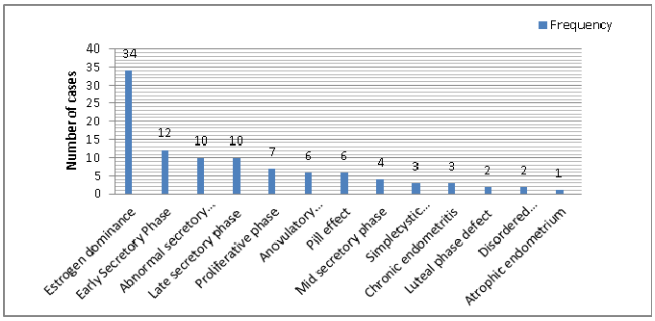

Figure 1: Frequency of endometrial pathologies (n=100)

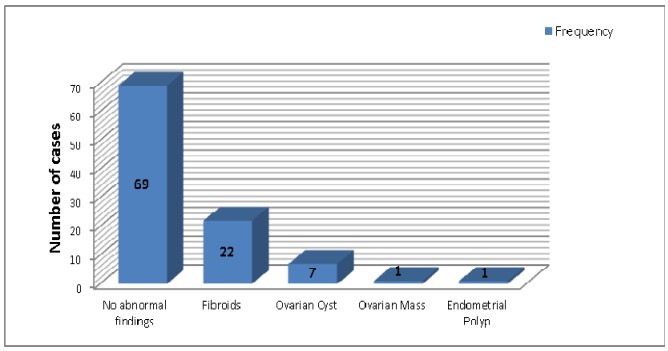

Figure 2: Frequency of patients related to Ultrasound findings (n=100)

In 33 % cases the endometrial curetting biopsies were non diagnostic; among these 26 cases revealed secretory phase endometrium which were further stratified into early secretory (12 cases), mid secretory (4 cases) and Late secretory phase endometrium (10 cases) as shown in Figure 1. Seven cases showed proliferative phase endometrium. There were 10 cases of abnormal secretory phase endometrium which showed discrepancy between glandular and stromal morphology. (Figure 1)

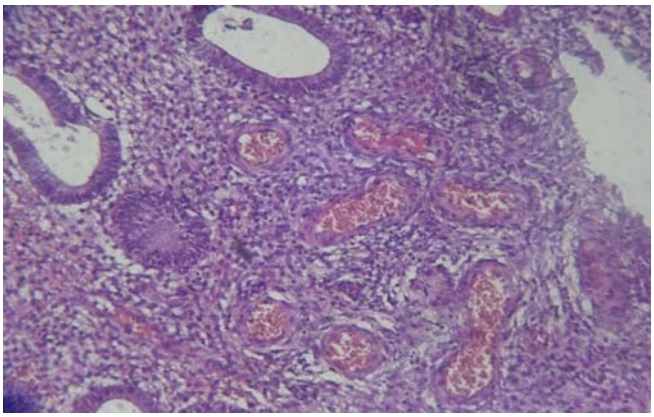

Figure 3: Estrogen dominance pattern showing focal clusters of thickened blood vessels. H&E stain x 400.

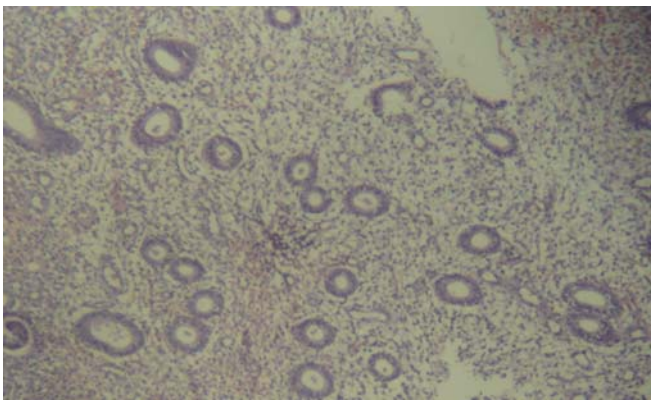

Figure 4: Anovalatory endometrium showing round to oval glands lined by single layered epithelium, stromal edema and hemorrhages. H & E stain x 400.

Anovulatory endometrium was the third most common pathology representing 6 cases. (Figure 1 & 4) Morphological findings were based on the presence of many thin walled blood vessels, areas of hemorrhages, edema along with inactive or weakly proliferative glands in a stromal breakdown.

An equal number of patients (6 cases) of pill-effect endometrium were seen. (Figure 1) Morphologically the pill-effect endometrium showed small glands with stromal decidualization. (Figure 4)

Out of 3 cases of endometritis 2 cases were diagnosed as tuberculous endometritis which morphologically showed chronic granulomatous inflammation with multinucleated giant cells. One case was diagnosed as chronic non-specific endometritis which could still be tuberculosis as chronic endometritis until proven otherwise should be considered tuberculous.

Among 100 patients, 31 patients had ultrasonographic study in which 22 patients had fibroids, 7 cases had ovarian cyst, 1 case was of ovarian mass and 1 case was of endometrial polyp. (Figure 2) The endometrial biopsies in 55 out of 100 patients were correlated with Last menstrual cycle (LMP) dates while 45 patients had taken hormone or had fibroids.

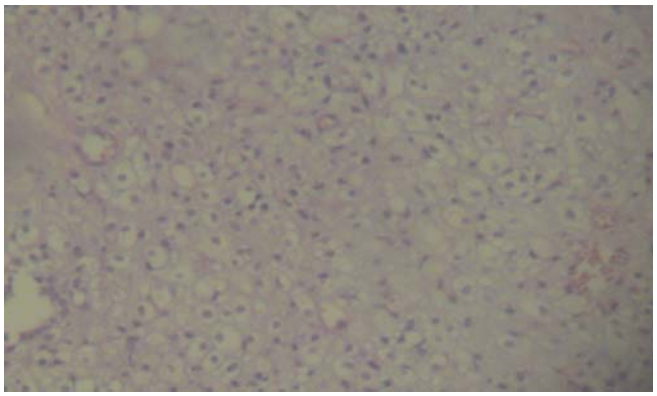

Figure 5: Pill effect endometrium showing decedualized stroma and edema and hemorrhages. H & E stain x 400

12 patients had infertility out of which 8 patients had primary and 4 patients had secondary infertility. Among primary infertility cases 3 patients showed estrogen dominance, 2 patients showed abnormal secretory phase, 2 patients showed late secretory phase with no diagnostic abnormalities, and one patient had chronic endometritis.

There were four patients with history of secondary infertility out of which one showed estrogen dominance, one patient had abnormal secretory phase and two patients had tuberculous endometritis.

Most of the patients were in the age of 20 to 50 years with mean age of 37 years. The age range in the largest group i.e. estrogen dominance was 20 to 60 years but most of the patients were in the age group of 30 to 40 years and this was the common age group in which endometrial biopsies was done.

The second most common pathology found in the patients was abnormal secretory phase endometrium with the age range of 20 to 40 years. (Table 1)

Table 1: Frequency of endometrial diagnosis related to age groups *(n=100)*

Diseases	20-30 Years	31-40 Years	41-50 Years	51-60 Years	Total Percentage
Estrogen dominance	7	16	10	1	34 %
Abnormal Secretory Phase	5	3	2	_	10 %
Anovulatory endometrium	3	1	2	_	6 %
Pill effect	2	2	2	_	6 %
Chronic Endometritis	2	1	_	_	3 %
Simple Cystic hyperplasia	_	2	1	_	3 %
Leuteal Phase Defect	_	1	1	_	2 %
Disordered Proliferative Phase	_	1	1	_	2 %
Atrophic	_	1	_	_	1 %
Non Diagnostic	5	13	14	1	33%
Total	24	41	33	2	100 %

Most of the patients of anovulatory bleeding were also in the age group of 25 to 35 years. (Table 1) The patients of chronic endometritis were in the age range of 20 to 40 years. (Table 1)

Patients with abnormal uterine bleeding due to pill-effect endometrium were in the age range of 20 to 40 years. (Table 1) One patient was diagnosed as atrophic endometrium. Her age was 35 years.

The frequency of patients with abnormal menstrual cycle was also noted. Out of 100 cases, 80 patients had

irregular menstrual cycle while 20 patients had regular but heavy menstruation. (Figure 6)

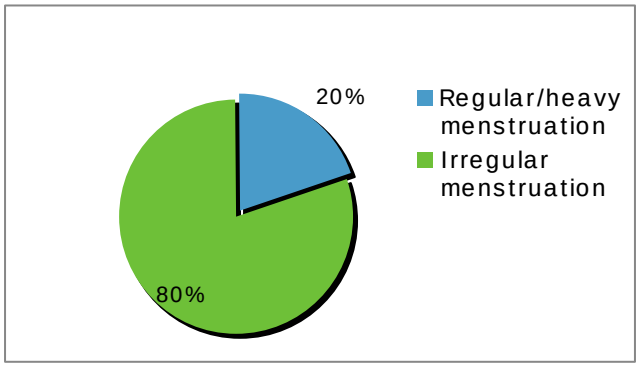

Figure 7: Frequency of patients with abnormal Menstrual Cycle (n=100)

Discussion

Endometrium is a hormonally sensitive and responsive tissue of the body[5]. The response of endometrium to stimulation by endogenous or exogenous steroid hormones is predictable [6]. Endogenous response is a reflection of the hypothalamic–pituitary-ovarian axis. Understanding of the complex interaction of this relationship between these structures is important [7]. The changes in the endometrium can be evaluated by histological, cytological and histochemical examination of the endometrial biopsies.

The objective of this study was to evaluate endometrial biopsies in the patients of abnormal uterine bleeding. For this purpose 100 cases of endometrial biopsies were studied at Pathology Department, Pakistan Institute of Medical Sciences Islamabad, over a period of 6 months from February 2010 to August 2010. We observed spectrum of morphological changes in these biopsies. Out of these 100 patients, we found eight patterns of endometrial abnormalities which were responsible for abnormal uterine bleeding. These included estrogen dominance (34%), abnormal secretory phase (10%), pill-effect (6%), anovulatory endometrium (6%), chronic endometritis (3%) simple cystic hyperplasia (3%), luteal phase defect (2%)and atrophic endometrium (1%). (Figure 1)

Nosheen Yousaf et al. reported normal phase of menstrual cycle was in 26.27% of patients followed by adenomatous hyperplasia (22.9%), cystic hyperplasia (17.9%), hormonal imbalance (14.76%), endometritis (10.2%), polyp (3.21%) and pill-effect endometrium (2.8%) cases[8].

In another study of 458 cases of abnormal uterine bleeding anovulatory cycle was seen in 22.9% cases followed by endometrial hyperplasia (11.1%), benign polyps (8.9%), endometritis (3.28%) and atrophic endometrium (1.6%) cases[9].

A study of dysfunctional uterine bleeding done by Vakiani M et al, on 1282 cases of endometrial biopsies showed that there were anovulatory cycle in 984 (77 %) of the patients and ovulatory cycle in 294 (23 %) of the patients. 948 (74 %) of the 1282 patients studied were at the climacteric i.e. perimenopausal. They concluded that dysfunctional uterine bleeding was found more often at the climacteric and mainly in the form of anovulatory endometrium. 88.14% of the cases (1130 patients) presented histological signs of estrogen dominance in the form of either anovulatory endometrium or ovulatory endometrium with cystic hyperplasia[10]. Their findings are in parallel with our findings. (Figure 1) In our study maximum number of endometrial curettings were done at the age group of 31-40 years (41%) followed by 41-50 years (33%), 20-30 years (24%). (Table 1) Todorovic et al. study showed that maximum number of curetting were performed in perimenopausal age (41-50) years [11].

Estrogen dominance pattern was the most frequent observation in almost all age groups. (Table 1) This is similar to the findings of Vakiani M et al[10]. In our study most of the patients of estrogen dominance pattern were present between 30 to 50 years of age. This study correlated with the study reported by Stickler, whose patients were between 30 to 45 years of age. The cause was described as increase level of uterine prostaglandin production [12]. High levels of estrogen eventually lead to hyperplasic endometrium with formation of polyps.

Cases of anovulatory cycle were the third most common diagnosis in our study and number of diagnosed patients were 6. Their age were ranged from 20 to 50 years. This study correlates with the observation made by Kailas who explains perimenopause as the transition from normal

ovulation to an ovulation which then eventually leads to permanent loss of ovarian function[13]. Another study done by Burger et al concluded that the occurrence of cycle irregularity is associated with an increasing frequency of anovulatory cycles in peri and postmenopausal women. While normal menstrual cycle close to menopause is associated with normal ovulation [14].

The mechanism causing ovulatory and anovulatory uterine bleeding has been described by Fraser et al. They found that ovulatory bleeding is associated with a series of vascular and hemostatic disturbances that contribute to increased loss of blood and tissue fluid and hence associated with disturbances of endometrial histology, vascular morphology and fragility with variable and increased blood flow [15].

In this study, 10 patients were given hormone replacement therapy, 4 patients had used intrauterine contraceptive device and 4 patients underwent bilateral tubal ligation. These patients were in reproductive age group and some of them were perimenopausal. All these women revealed history of irregular bleeding. Ten cases were diagnosed as abnormal secretory phase. A study done by Urmila Kella et al revealed that a high proportion of women use contraceptives improperly and this leads to hormonal imbalance [16].

Chronic endometritis has been observed in 3–10% of women with irregular uterine bleeding who undergo endometrial biopsy. It is not an uncommon finding in endometrial curettage specimens and in most cases a specific cause can be identified such as pelvic inflammatory disease, uterine leiomyomas, an intrauterine device, or postabortal and postpartum states [17, 18, 19].

In our study 3% patients were diagnosed as chronic endometritis. This observation is comparable with Buckley CH et al who studied 359 biopsies of endometrium and showed that there were 3.4% cases of chronic endometritis [20]. One patient of chronic nonspecific endometritis was a 30 years old lady with secondary infertility and two patients were diagnosed as chronic granulomatous inflammation with history of primary infertility. A similar study reported by Ayesha Yousaf et al showed that 10% out of 50 infertile patients had tuberculous endometritis [21]. A study done on infertile patients in India by Zawar MP et al showed that 2.6% of infertility were due to tuberculous endometritis [22].

Stromal changes were also noted in which one case of tuberculosis showed secretory exhaustion while that of nonspecific chronic inflammation also showed secretory exhaustion. Stromal edema and mitosis was present in all cases [23, 24].

In the present study 34% cases of hormonal imbalance were identified. Major features of these cases showed various aspects like tortuousity and dilatation of glands. As estrogen causes endometrial growth, increase in size and tortuosity (twisting) of the uterine glands, and increased thickness and blood supply of the uterine mucosa. Similarly progesterone is also associated with increase in tortuosity. So abnormal gland appearance such as tortuousity and gland dilation could be attributed to abnormal release of estrogens and progesterones [25].

Approximately 90% of cases of dysfunctional uterine bleeding are secondary to anovulation [26]. Without ovulation, the corpus luteum cannot form and subsequently there is inadequate progesterone secretion. The resulting unopposed estrogen allows the endometrium to proliferate unimpeded. This overgrowth of the endometrial lining finally outgrows its blood supply and degenerates resulting in asynchronous breakdown of the lining at different levels and heavier than usual bleeding. Some potential causes of anovulatory uterine bleeding include excessive exercise, emotional stress, eating disorders, polycystic ovarian syndrome (PCOS), obesity, and thyroid disease [26].

In our study one case was found to be of atrophic endometrium. In one study it was observed that Atrophic endometrium is associated with down regulation of estrogen receptor alpha (ER-α) [27]. So atrophic endometrium identified in current investigation could be attributed to down-regulation of ER-α due to hormonal changes.

Conclusion

In the current available investigations endometrial biopsy is the most reliable source to diagnose

endometrial pathologies responsible for abnormal uterine bleeding.

Estrogen dominance was the most common cause for abnormal uterine bleeding affecting almost all age groups and if we include other pathological entities like abnormal secretory phase endometrium, anovulatory endometrium, pill-effect endometrium, simple cystic hyperplasia it will lead to a huge number of cases of hormonal imbalance.

A significant number of endometrial curetting biopsies (About 33%) did not show any diagnostic abnormalities. This may be due to sampling errors as lower uterine segment endometrium may not be that representative in terms of hormonal effects. Errors of biopsy interpretations and history may also be responsible for inaccurate correlation. Complete clinical history is very important in this regard especially last menstrual period (LMP) and use of hormonal therapy has a crucial role in the diagnosis of endometrial biopsies.

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