Study of Histopathological changes of Endometrium in Abnormal Uterine Bleeding

Aruna Kumari Pagalla¹, Shyam Sunder Kasapa²

ABSTRACT

Aims and Objective : To find out various Histopathological changes in Abnormal Uterine Bleeding in different age groups presenting with various bleeding patterns and to give correct clue to the clinician for the proper management of patients.

Materials and Methods: The present study was conducted in the Department of Pathology, at a tertiary care hospital in Karimnagar over a period of 2 years. A total of 116 aged with AUB was included. D&C, endometrial biopsy, aspiration, single curettage are used.

Results: The most common age group presenting with AUB was 41-50 years (44 %). Normal cyclical pattern - 60 cases, disordered proliferative endometrium - 1 case, Atrophic endometrium - 7 cases, the commonest pathology irrespective of age groups was hyperplasia’s - 14 cases. Other causes identified were complications of pregnancy - 5 cases. Benign endometrial polyp - 9 cases. Endometrial adenocarcinomas - 3 cases. Chronic endometritis - 1 case.

Conclusion: Endometrial causes of abnormal uterine bleeding are age related pathology. Histopathological examination of endometrial biopsy and hysterectomy specimens gives major diagnostic tool for evaluation of AUB and specific diagnosis could help the physicians for the successful management of AUB.

Keywords: Endometrial hyperplasia, menorrhagia, adenomyosis, polyps, carcinoma

INTRODUCTION

Abnormal Uterine Bleeding (AUB) is defined as any bleeding that does not correspond with the frequency, duration or amount of blood flow of a normal menstrual cycle and could be a sign of simple hormonal imbalance or a serious underlying condition necessitating aggressive treatment including a major surgical procedure.

The causes for AUB can be categorized into: (A) Organic, such as genital tract infections, tumors (benign or malignant), Adenomyosis, pregnancy and its complications, systemic disorders and iatrogenic accounting for 20% of cases; (B) Dysfunctional Uterine Bleeding (DUB) caused by anovulation or oligoovulation is responsible for 80% of menorrhagia & diagnosed after exclusion of all conditions enumerated in (A). Anovulation and oligoovulation resulting in hyperestronism, cause prolonged stimulation of the endometrial lining and increase the risk of both endometrial hyperplasia and carcinoma.

Women suffer from many gynecological diseases. One among them is Abnormal Uterine Bleeding (AUB), having significant morbidity as it interferes with their personal, family and social life. Women of present generation experience more menstrual cycles than her ancestors did. This is mainly due to decreased parity and reduction in lactational amenorrhea.

Advancements in medicine combined with increasing awareness of gynecological problems, women are gaining more awareness to most of the diagnostic and therapeutic modalities. The endometrial biopsies and hysterectomy specimens are chosen to evaluate Abnormal uterine bleeding as it is having several advantages over other diagnostic methods.

The hormonal assay is very expensive and laboratories having facilities of hormonal assay are not available in all places. Ultrasonography as a diagnostic tool has
limited value in AUB except in atrophy and hyperplasia. Other investigations like Dilation and curettage, hysteroscopy guided biopsies and saline infusion sonographic biopsies are mainly helpful in diagnosing organic pathology.

MATERIALS AND METHODS

The retrospective study was conducted in the Department of Pathology, at a tertiary care hospital, CAIMS Karimnagar over a period of 2014 to 2016. A total of 116 aged with AUB was included.

Dilatation of the Cervix and Curettage

The traditional method of removing endometrium for pathological Examination is by dilating the cervix and methodically scraping tissue from the anterior and posterior walls of the uterine cavity with a curette. Curettage is most appropriate when a pathological process is suspected, for example for the diagnosis of hyperplasia or carcinoma, but, equally, provides an excellent sample for the assessment of the endometrial response to hormonal stimulation. In some cases, for example in complete abortion, curettage is actually undertaken for therapeutic rather than diagnostic purposes.

Information about Endocervical extension of an endometrial neoplasm can be obtained by performing a fractional curettage (i.e., a separate sampling from the endometrial and Endocervical cavities during the same procedure).

Regeneration of the endometrium proceeds very rapidly after curettage. Complete restoration occurs in 2 or 3 days in most instances. Exceptionally intrauterine adhesions develop, resulting in amenorrhea and other menstrual abnormalities. This condition, known as “Asherman’s syndrome,” is seen most often after postpartum or curettages and is thought to be the result of a subclinical uterine infection.

Endometrial Biopsy

It is a safe alternative to dilation and curettage for the evaluation of infertile or dysmenorrhic patients. Kahler et al., in their study of 160 patients demonstrated that when the endometrial biopsy was performed successfully (137 patients), the tissue obtained was truly representative of the endometrium in all but six, as proved by subsequent dilation and curettage of hysterectomy.

Single Curettage

The falling of a single strip of the endometrium from the anterior or posterior uterine wall, without cervical dilatation is a particularly suitable technique for examination of the endometrium in patients with infertility. It causes minimal cervical and endometrial damage but allows, in the well orientated sample, fair and accurate assessment of the state of the endometrium as hormone induced changes usually develop relatively uniformly throughout this tissue (Johansson et al 1982).

It causes so little disturbance to the endometrium that repeat biopsy can be carried out in the same cycle.

Aspiration, Washes and Endometrial Brush Techniques

Aspiration and endometrial wash techniques can be identification of a pathological process which may affect the entire endometrium. The specimens tend to be small, are often fragmented and may, therefore, be very difficult to orientate, they are, in some cases, more suitable for examination by cytopathological than histopathological techniques.

Fixation of Endometrial Biopsies

Buffered Formation Solution: However poorly penetrating, it is preferred for larger pieces of tissue, such as bulky polyps.

Processing Techniques:

1. Paraffin Processing:

Most commonly endometrial biopsies are paraffin processed and sections, cut at 4 to 5 microns, are stained with hematoxylin and eosin. Some pathologists also like to examine a connective tissue stain, such as van-gieson, but it is not put practice to do so routinely.

PAS/Alcian blue stains, with and without prior digestion by diastase, are useful of the identification of glycogen, histiocytes (in inflammatory process) and main in both neoplasm and metaplastic foci. Gram stain for bacilli, zielhneelson stains for acid/alcohol fast bacilli and van kossa stain for calcium are also useful in their place, However the range of stains used in the outside reporting of endometrial biopsies is very small.

2. Frozen Sectioning:

Frozen sections, stained with hematoxylin and eosin, may be hysterectomy, when they are used to determine whether a non-neoplastic endometrial condition for which simple hysterectomy alone will suffice is or if there is an endometrial neoplasm which necessitates hysterectomy and bilateral salpingo-oophorectomy with nodal dissection. There are, however a number of immunohistochemical techniques which frozen rather than fixed 113 tissues and many monoclonal antibodies will give satisfactory, result only on frozen material.
3. Electron Microscopy:

Electron microscopy is seldom required in the diagnosis of routine endometrial samples. Its use appears to be limited to the recognition of the occasional purely differentiated neoplasm and even here its contribution is minimal.

4. Immuno Histochemistry:

Immunohistochemical examination of the endometrium is undertaken most frequently for the identification of neoplastic conditions, both frozen material and paraffin processed tissue are suitable for this purpose.

Timing of Endometrial Biopsy:

The request form should provide the date of the last menstrual period and preferably the date of ovulation or basal temperature change. The information concerning the use of any steroid hormones, mode of contraception, use of any drugs known to interfere with the normal secretion of trophic hormones, details of any endocrinological disease and past medical history.

The best time for observing cyclical changes in the endometrium is between 7 and 11 postovulatory days. At this stage it is possible to assess both the adequacy of the secretory change and its uniformity. It should also be possible to identify an inflammatory process if it is present, although tuberculosis may be difficult or impossible to recognize until the 12 or 13 postovulatory day.

Site of the Endometrial Biopsy:

Endometrial biopsies should be taken from the anterior or posterior wall in the uterine body where cyclical changes are likely to be most adequately developed. The tissue of the uterine isthmus fails to undergo cyclical changes and a common error of the inexperienced surgeon is to take sample of the endometrium too low down in the cavity. Basal endometrium also fails to show normal cyclical changes and therefore the immediate postmenstrual biopsy may fail to provide useful information.

The endometrium overlying a submucous leiomyoma contains fewer single layer of columnar epithelium with a little underlying stroma. The tissue in this area may also be ulcerated or focally inflammed. In the patient wearing an intra uterine contraceptive device removal of tissue from the contact site may give a false impression of infection, irregular ripening or scarring.

METHODOLOGY

Inclusion Criteria

The specimens received in the Department of Pathology belonging to cases of Abnormal uterine bleeding attended in the Department of Obstetrics and Gynecology, CAIMS, Karimnagar. The specimens of hysterectomy presented with Abnormal uterine bleeding were also included in this study, pertaining to the endometrium only.

Exclusion Criteria

Number of cases: 100 cases were studied, exclusively of isolated endometrial pathology.

Method of Collection of Data:

The study material consisted of endometrial curetting and Hysterecctomy specimens from 100 patients from Department of Obstetrics and Gynecology, CAIMS between November 2014 to October 2016. These patients were having a clinical diagnosis of Abnormal uterine bleeding. Endometrial curetage samples and tissue sections were fixed in 10% formalin and processed. Histopathological slides were prepared with Haematoxylin and Eosinstaining. Special taining like Periodic acid-Schiff staining(PAS) and reticulin was performed when warranted.

RESULTS

The most common age group presenting with AUB was 41-50 years (44 %).

- Normal cycling pattern – 60 cases
- Disordered proliferative endometrium-1 case
- Atrophic endometrium- 7 cases
- The commonest pathology irrespective of age groups was hyperplasia –14 cases.
- Other causes identified were complications of pregnancy – 5 cases.
- Benign endometrial polyp –9 cases.
- Endometrial adenocarcinomas-3 cases.
- Chronic endometritis –1 case.

Endometrial causes of AUB and age pattern was statistically significant with p value of <0.0001. There is age specific association of endometrial lesions. In perimenopausal women AUB is most commonly dysfunctional in origin and then in reproductive age group one should rule out complication of pregnancy. The incidence of normal proliferative endometrium was significantly high in this study, suggesting an early presentation of these patients.

NON-UTERINE CAUSES

1. Coagulation disorders
2. Endocrine disorders
3. Liver
4. Exogenous hormones

**UTERINE CAUSES**

1. Autolysed specimens
2. Leiomyomas
3. Cervical pathology
4. Adenomyosis

The table depicts the distribution of 100 cases of AUB with isolated endometrial lesions according to age group in the present study. Different Histopathological types of endometrial patterns were studied. Normal cyclical pattern 60 cases, disordered proliferative pattern 1 case, hyperplasia 14 cases, atrophic pattern 7 cases, benign endometrial polyp 9 cases, chronic endometritis 1 case, endometrial carcinoma 3 cases, and complications of pregnancy 5 cases.

**DISCUSSION**

Normal menstruation is defined as bleeding from secretary endometrium associated with an ovulatory cycle not exceeding a length of five days. Any bleeding not fulfilling these criteria is referred to as an Abnormal Uterine Bleeding.

The causes of Abnormal Uterine Bleeding include the wide spectrum of diseases of the reproductive system and non-gynecological causes. Organic causes of Abnormal Uterine Bleeding may be sub divided into reproductive tract diseases, iatrogenic causes and systemic diseases.[4]

When an organic cause of AUB cannot be found, then by exclusion, a diagnosis of DUB is assumed. In about 40% of patients the AUB is the result of well-defined organic abnormality. The routine non-invasive investigations for AUB include complete blood count, platelet count, and prothrombin time, activated partial thromboplastin time and liver function tests. In women of reproductive age group serum and urine human chorionic gonadotrophin levels are evaluated to rule out pregnancy. To rule out endocrinal etiology, thyroid function tests, Follicular stimulating hormone, luteinizing hormone, prolactin levels are assessed. To rule out these causes imaging studies such as pelvic ultrasound transvaginal ultrasound and tissue sampling.

Dilatation and curettage can be diagnostic as well as therapeutic procedure.[5] The sensitivity of endometrial biopsy for the detection of abnormalities is about 96%. The most likely etiology of DUB relates to the patients age, as to whether the pt is pre menopausal, perimenopausal, post menopausal.[6]

Neonatal females may have spotting for few days due to withdrawal of maternal estrogen, which had stimulated endometrium in uterus, resolve within few days after hormone levels comes down. After this age precocious puberty and functional ovarian tumors to be considered.[7] Two patients below the age of 20 years showed normal cyclical endometrium pattern. The prevalence of primary coagulation disorders in adolescents requiring hospitalization is 3-20%. Hence all adolescents with menorrhagia should undergo evaluation for coagulopathy.[8] Complications of pregnancy were common in the age group of 21 to 30 years. This can be explained by the fact that most women conceive at this age, hence pregnancy should be excluded in this age group with urine gravindex test.[9]

My study significantly revealed that the occurrence of menstrual disorders increases with advancing age. The commonest age group presenting with excessive bleeding was 41 to 50 years. [9, 10] The reason for increased incidence due to climacteric period. In my study proliferative lesion like disordered proliferative endometrium, hyperplasia’s, benign polyps are also more common in this age group.[10]

When women reaches menopause, cycles shorten and anovulatory due to decline in follicles and estradiol levels. Women with 51 to 70 years were less when compared to 41 to 50 years because they must be evaluated and treated early.

Predominant number of cases in this study showed normal physiological changes such as proliferative, secretary and anovulatory changes. An abnormal physiological change includes pill endometrium, irregular shedding and decidualisation.

Bleeding in the proliferative phase may be due to anovulatory cycles and in secretary phase ovulatory dysfunctional uterine bleeding.

Disordered proliferative pattern seen in one case in 31 to 40 years. Illies in the spectrum, at one end of proliferative lesion of endometrium to carcinoma at other end with intervening stages of hyperplasia’s. The endometrial pattern is hyperplastic but without increase of endometrial volume and also refers to proliferative phase of endometrium but does not fit in any day of menstrual cycle.[11]

It is not enough to be considered hyperplastic and it resembles focal hyperplasia rather than diffuse hyperplasia. Diagnosis at early stage of the spectrum will be of definite help to prevent the disease progression.[12] (FIG 5).

Atrophic endometrium is more in 51 to 70 years age. The cause of bleeding may be due to anatomic vascular variations or local abnormal hemostatic mechanisms. Thin
walled veins, superficial to the expanding cystic glands make the vessels vulnerable to the injury.\textsuperscript{[13]}

The number of hyperplasia’s in this study is 14 cases. Identification of endometrial hyperplasia’s is important because they are thought to be precursors of endometrial carcinoma.\textsuperscript{[14]}

The number of benign endometrial polyps in this study is 9 cases, incidence is more between 31 to 50 years. Lower incidence in young age is group is attributed to possible spontaneous regression, which is characteristic of cycling endometrium in reproductive age group.

There is a significant difference between the endometrial polyp and normal endometrium in receptor expression, cell proliferation and apoptosis regulation. These differences combined with nonrandom chromosomal abnormalities and monoclonality also suggests that the polyp may provide a suitable micro environment for the development of malignancy.\textsuperscript{[15]}

The incidence of carcinoma endometrium was more between 41 to 60 years 3 cases. The low incidence of endometrial cancer in this study may be attributed to the practice of early child bearing and multiparty.\textsuperscript{[16, 17]}

AUB of conditions related to pregnancy formed a significant group in young age. In reproductive age complications of pregnancy should be ruled out. Chronic endometritis was observed only in one case, presented with AUB and pelvic pain.

The commonest bleeding patterns were menorrhagia about 43%, Metrorrhagia 30%, polymenorrhagia 22%, Oligomenorrhoea 2%, post menopausal bleeding 3%.

Most of the patients in normal cyclical pattern, presented with menorrhagia, polymenorrhagia, continuous bleeding. In endometrial hyperplasia’s commonest bleeding pattern was menorrhagia and continuous bleeding. In pregnancy related, commonest type of bleeding was continuous. In endometrial carcinoma most common type was Metrorrhagia, also continuous.

CONCLUSION

Endometrial causes of abnormal uterine bleeding where age related pathology. Histopathological examination of endometrial biopsy and hysterectomy specimens gives major diagnostic tool for evaluation of AUB and specific diagnosis could help the physicians for the successful management of AUB.

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**Table 1: Distribution of Cases Presenting With AUB**

<table>
<thead>
<tr>
<th>Total Number Of Cases Received</th>
<th>116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated Endometrial Pathology</td>
<td>100</td>
</tr>
<tr>
<td>Leiomyoma ± Endometrial Pathology</td>
<td>9</td>
</tr>
<tr>
<td>Cervical Pathology</td>
<td>1</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 2: AUB with isolated endometrial lesions according to Age group**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-70</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Cyclical Patterns</td>
<td>2</td>
<td>7</td>
<td>22</td>
<td>29</td>
<td>-</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>Disordered Proliferative Pattern</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>Atrophic Pattern</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Benign Endometrial Polyp</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Chronic Endometritis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Endometrial Carcinoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Complications Of Pregnancy</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3</td>
<td>12</td>
<td>32</td>
<td>44</td>
<td>7</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

The commonest bleeding patterns were menorrhagia about 43%, Metrorrhagia 30%, polymenorrhagia 22%, Oligomenorrhoea 2%, post menopausal bleeding 3%.
Figure 1: Late Proliferative Endometrium H&E X 40 X
Figure 2: Cystic atrophy H &E x 40x
Figure 3: Simple atypical hyperplasia H&E x 40x
Figure 4: Corpus luteal defect H&E x 40x
Figure 5: Disordered proliferative endometrium H&E x 40x
Figure 6: Simple hyperplasia H&E x 40x
Most of the patients are under low socio-economic group in present study. Both quantitatively and qualitatively gynecological pathology form a bulk of Histopathology specimens in any teaching institution or other diagnostic laboratory dealing with histopathology. While the medical health and non-medical population give major importance to cervical biopsy and cervical carcinoma, millions of women from menarche to menopause and in their post-menopausal as well as senile age groups go to the gynecology with a variety of symptoms related to ovarian endometrial function. The only way to diagnose the cause of their symptoms is the examination of endometrial tissue. This can be done by studying the endometrial biopsies.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

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REFERENCE


