International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2022; 5(1): 11-16
Received: 06-11-2021
Accepted: 10-12-2021

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Histopathological spectrum of endometrium in hysterectomy specimens from cases of abnormal uterine bleeding

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DOI: https://doi.org/10.33545/pathol.2022.v5.i1a.446

Abstract
Introduction: In India, the prevalence of women suffering from abnormal uterine bleeding is around 17%. Dilatation and curettage, endometrial biopsy and hysterectomies play an important role in diagnosis as well as treatment of abnormal uterine bleeding cases. Though number of minimaly invasive surgical options available, hysterectomy remains the widely accepted and practiced treatment of choice. Therefore those cases where causes of bleeding cannot be determined clinically then histological examination of hysterectomy specimen required to establish the etiology of abnormal uterine bleeding.
Material and Methods: This was a prospective study conducted for a period of two years in department of pathology in tertiary care hospital, GAIMS, G.K.General hospital, Bhuj, Kutch region in India. Total of 300 women presenting with abnormal uterine bleeding on whom consecutive hysterectomy done were included in the study. Gross examination done and H&Estained section were studied and analyzed according to publish protocols.
Results: Total of 495 hysterectomy, 300(61%) of patients presented with abnormal uterine bleeding.86/300(29%) presented with heavy menstrual bleeding. Proliferative phase is the most common histological finding with 128/300(42%), endometrial hyperplasia in 40/300(13%), endometrial carcinoma in 2/300(1%) of women.
Conclusion: Abnormal uterine bleeding is age related pathology with common symptom amongst women. Even though medical treatment and conservative surgeries have emerged, hysterectomy is the definitive treatment modality for abnormal uterine bleeding in developing and affluent countries. All hysterectomy specimens even if it appears grossly normal should be subjected for histopathological examination regardless of the preoperative diagnosis, as unsuspected incidental findings can be found in these specimens.

Keywords: Abnormal uterine bleeding, hysterectomy, endometrial histopathological examination

Introduction
Endometrium is the inner lining of uterine cavity, it undergoes dynamic physiologic and morphologic changes during menstrual cycle in response to sex steroid hormones secreted by ovary [1]. In a normal menstrual cycle there is an interval of 28 ± 7 days with 4 ± 3 days duration and blood loss amounting to 30 ml to 80 ml/cycle. Abnormal uterine bleeding (AUB) is a symptom and not a disease and is said to occur when bleeding differs in frequency, duration and in amount during normal menstrual cycle or after menopause. Earlier AUB was described by terms such as menorrhagia, dysfunctional bleeding, oligomenorrhea; now these terms are abandoned. Currently AUB has been updated to standardized the nomenclature [2]. In early 2011, FIGO published new classification for causes of abnormal uterine bleeding among women of reproductive age group [3]. Etiologies of AUB include anatomic causes, hormonal dysfunction, infections, systemic diseases, medications and pregnancy complications [4].
In India the prevalence of women suffering from AUB is around 17% [5]. Statistical data from our institute shows that around 30 % of patients visiting obstetrics and gynecology outpatient department suffers from one of the causes of AUB. Amongst the various causes of AUB-PALMCOEIN (Polyp, adenomyosis, leiomyoma, malignancy, coagulopathy, endometrial causes, iatrogenic and not otherwise specified); structural causes such as leiomyoma, adenomyosis, endometrial hyperplasia and isolated endometrial pathologies are

more common in frequency [3]. Dilatation and curettage (D&C) and endometrial biopsy play an important role in diagnosis as well as treatment of AUB cases. Management of abnormal uterine bleeding is tailored according to individual women's therapeutic goals, desire for conception, underlying medical conditions and tolerance to side effects. Prolonged bleeding can be financial burden to already economically constrained family with extra-expense of medical supplies and lost work time. A number of minimally invasive surgical options for hysterectomy do exist now and are promising like endometrial ablation, thermal balloon therapy and uterine artery embolization but restricted availability and cost factor limit them from being widely used. Therefore, hysterectomy still remains the widely accepted and practiced treatment of choice. Hysterectomy is also the second most frequently performed major surgical procedures on women all over the world, next only to caesarean. In India few national statistics for hysterectomy is available, however incidence of hysterectomies found in Gujarat state and Haryana state range from 7-8% [6, 7].

Materials and Methods

The present prospective study "Histopathological Spectrum of the Endometrium in Hysterectomy Specimens in patients presenting with Abnormal Uterine Bleeding in Kachchh region of Gujarat" was conducted in the Department of Pathology, Gujarat Adani Institute of Medical Sciences, G.K. General Hospital, Bhuj, Kachchh.

Out of 495 hysterectomy specimens, a total of 300 women presenting with AUB on whom consecutive hysterectomy was performed for 2 years were studied.

The detail clinical history, results of relevant investigations were collected from the patient's case file and histopathology requisition forms received along with the specimens. All hysterectomy specimens were received in 10% formalin. Gross examination of the uterus was carried out according to protocol of surgical grossing for hysterectomy described by Rosai & Ackermann and Robert Kurmann [8, 9].

Tissue bits were processed in automatic tissue processor and paraffin embedded 5 microns sections were stained with Haematoxylin and Eosin (H & E) [10] were studied and analyzed.

Statistical averages and proportions will be calculated as per the requirement of the study.

Inclusion criteria: Women of all age groups with clinical diagnosis of abnormal uterine bleeding, undergoing hysterectomy is included in the study.

Exclusion criteria: Women with gestational causes, cervical, vaginal pathology, coagulopathy and other systemic causes of abnormal uterine bleeding is excluded.

Results

1. In 300 (61%) out of 495 patients, clinical diagnosis of AUB was made, hence results of these 300 specimen were analyzed.
2. The youngest patient presenting with AUB was 18 years old, while the oldest patient was 80 years old. Maximum number of patients 132/300 (44%) were in the age group of 41-50 years (perimenopausal age group).
3. Heavy menstrual bleeding was the most common presenting symptom accounting 86 (29%) out of 300 women. (Table 1)

Table 1: Shows distribution of cases according to bleeding pattern. (N=300)

Type of bleeding	No. of patients	Percentages (%)
Heavy menstrual bleeding	86	29
Heavy prolonged menstrual bleeding	20	6
Intermenstrual bleeding	74	25
Frequent menstrual bleeding	63	21
Postmenopausal bleeding	57	19
Total	300	100

4. Four patients out of 300 patients showed dual pathology thus a total 304 pathology were identified. Proliferative phase endometrium 128 (42%) formed the most common finding, followed by atrophic endometrium with 52 (17 %) and secretory phase endometrium 48 (16%) women.(Figure 1).

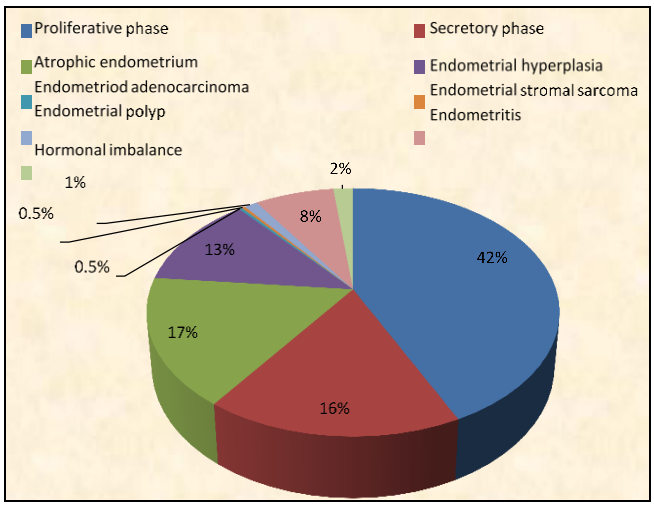

Fig 1: Showed histomorphological spectrum of endometrium. (N=300)

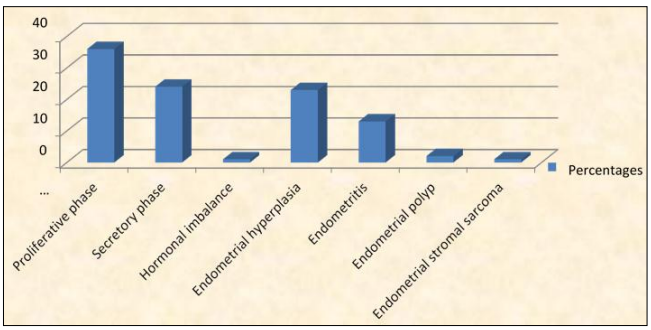

Fig 2: Shows histomorphology of endometrium in females with heavy menstrual bleeding (N=86)

5. 89 patterns of endometrial findings were observed in 86 women. In 3 females 2 patterns were observed. Endometrial hyperplasia was identified in 23% (20/97) women. The histomorphological patterns in postmenopausal bleeding was atrophic endometrium found in 41 (72%) females, in 10 cases showed proliferative phase. Endometrioid adenocarcinoma was found in one post-menopausal women.
6. Out of 300 patients, endometritis was observed in 24 (8 %) patients, which comprised of chronic endometritis in 19 (6%) females, acute endometritis in 2 women and acute on chronic endometritis in another 2 women each. One women shows granulomatous endometritis.

7. Table 2 showed dual histopathological changes in endometrium in 4 women. These are endometrial hyperplasia with chronic endometritis in two females, endometrial hyperplasia with polyp, polyp with chronic endometritis in one case each. The most frequent dual findings was in reproductive age group.

Table 2: Dual histomorphological findings in endometrium (N=4)

Patterns	31-40	41-50	Total
Eh+ch.en	2	-	2
Pol+ch.en	-	1	1
Eh+pol	1	-	1
Total	3	1	4

eh+ch.en- endometrial hyperplasia with chronic endometritis, eh+pol- endometrial hyperplasia with polyp, pol+ch.en- polyp with chronic endometritis, pp+pol- proliferative phase with polyp

8. The gross features of endometrium varies according to the etiology. In hyperplasia and malignancy, there is thickened endometrium. (figure 3,4). One polyp shown grossly depicted in figure 5. Rest most of have unremarkable gross which are included in our study.

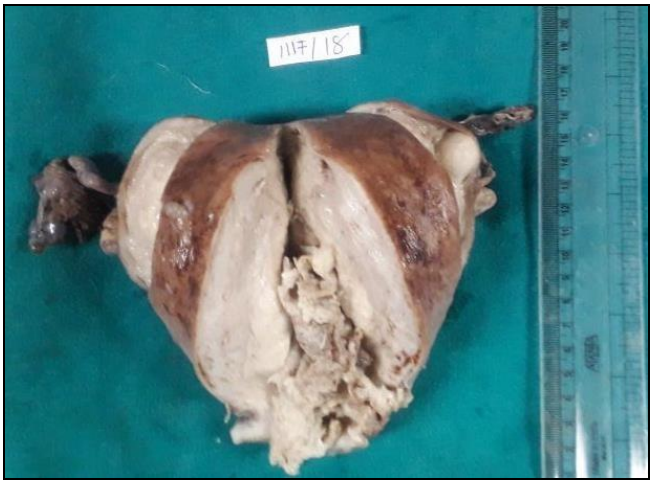

Fig 3: Uterine cavity shows papillomatous hyperplasia of the endometrium

Fig 4: Cut surface through uterus shows papillary tumour in the endometrial cavity. The tumour is greyish white in colour and extending up to external os.

Fig 5: Cut section of uterus shows endometrial polyp in the endometrial cavity

9. Microscopic examination, in cases of normal menstrual cycle consists of proliferative phase, secretory phase, menstrual phase and atrophic phase in the endometrium which shows its various histomorphological changes accordingly. Various etiology of benign nature consists of chronic endometritis having plasma cells infiltrate, endometrial polyp lined by structure on three sides and thickened blood vessels. Endometrial hyperplasia and endometrioid carcinoma and endometrial stromal tumor shows specific morphology. (figure 6- 10).

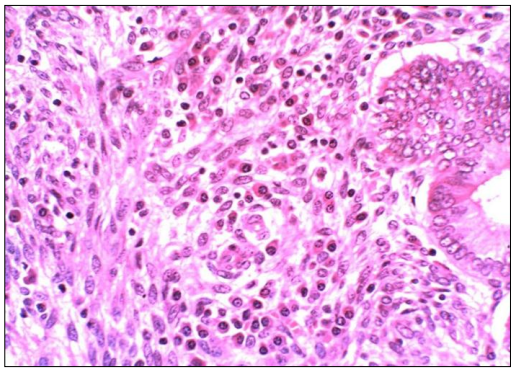

Fig 6: Histology of chronic endometritis shows numerous plasma cells in the endometrial stroma (H&E x400)

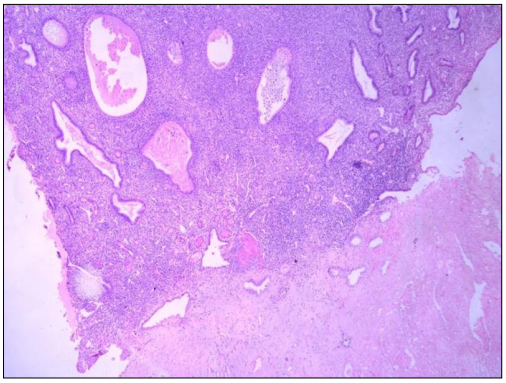

Fig 7: Histology of endometrial polyp showing cystically dilated and inactive atrophic endometrial glands, stroma shows dilated blood vessels. (H&E x 40)

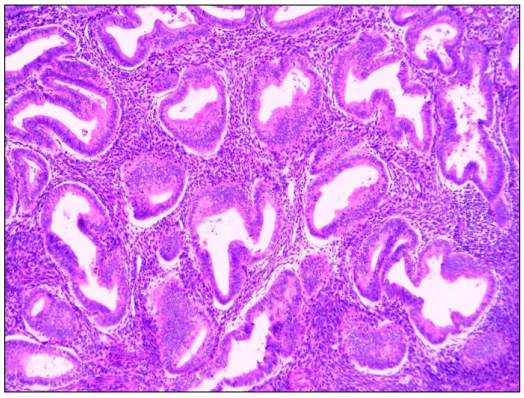

Fig 8: Histology of endometrial hyperplasia without atypia, shows crowded glands without pouching and 3-4 layers of epithelial stratification. (H&Ex100)

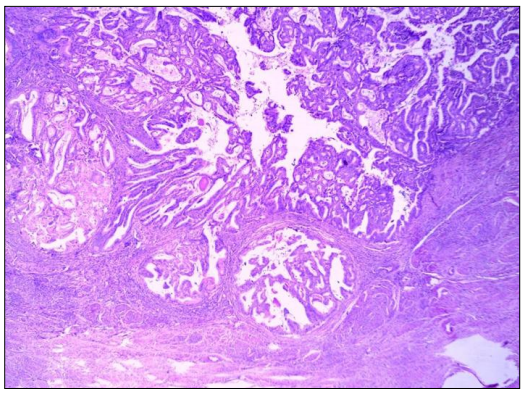

Fig 9 A: Histology of endometrioid carcinoma shows malignant cell arranged in papillary and glandular pattern (H&E x40)

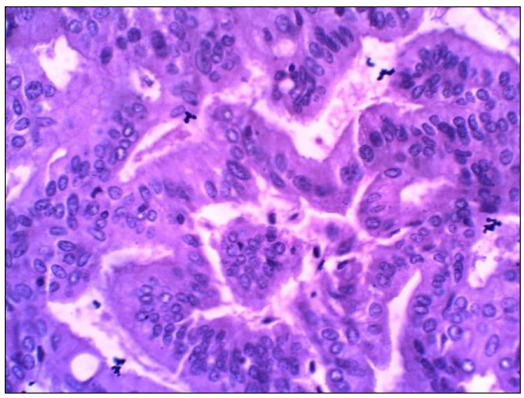

Fig 9B: Histology shows endometriod carcinoma comprised of villoglandular architecture lined by stratified columnar epithelium, containing granular eosinophilic cytoplasm, mild nuclear atypia with atypical mitosis (H&Ex400)

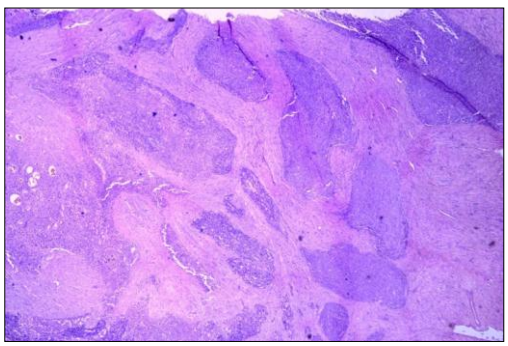

Fig 10: Histology shows low grade endometrial stromal sarcoma having cellular areas of spindle stromal tumour with infiltration in the myometrium (H&E x 40)

Discussion

Abnormal uterine bleeding (AUB) is the most common cause for women to consult a gynaecologist. The causes of abnormal uterine bleeding include a wide spectrum of diseases of the reproductive system and non-gynaecologic causes as well. Organic cause of abnormal uterine bleeding maybe subdivided, into reproductive tract disease, iatrogenic causes and systemic diseases. In about 20- 30% of cases, the abnormal uterine bleeding is the result of a well-defined organic cause [11]. Symptoms of AUB frequently co-exist with uterine fibroids, but the relationship between AUB and fibroids remains incompletely understood.A structured approach to establishing the cause using the FIGO - PALMCOEIN classification system facilitates accurate diagnosis and treatment options [3]. The present study was done to evaluate the histomorphology of endometrium in females with abnormal uterine bleeding undergoing hysterectomy. Several studies describing endometrial pathology in females with AUB cases are published in the literature [11-18].

The most common age group of females presenting with AUB was found in the age group of 41-50 years; in this group 132/300 (44%) female were found. The other studies of AUB showed age of presentation of 41-50 years in 33-59% patients [11-18]. The reason for increased incidence of abnormal uterine bleeding in this age group (41–50 years) may be due to the fact that these patients are in their climacteric period [12]. In our study however two females with AUB were below 20 years of age, of which one was mentally retarded and another had uterine malformation.

Various bleeding patterns are described in patients with AUB, these are heavy menstrual bleeding, irregular menstrual bleeding, infrequent menstrual bleeding, frequent menstrual bleeding, prolonged menstrual bleeding, intermenstrual bleeding, post-menopausal bleeding, precocious menstruation, acute AUB & chronic AUB. Amongst that, heavy menstrual bleeding is excessive menstrual blood loss which interferes with the woman's physical, emotional, social, and material quality of life, and which can occur alone or in combination with other symptoms. In this study we followed new recommended FIGO terminologies for describing bleeding patterns in patients with abnormal uterine bleeding, hence we have compared bleeding pattern in our patients with recently published reports [16, 17, 19].

Table 4: Comparison of bleeding pattern with different studies.

Authors	Year of publication	No. of cases	Commonest bleeding pattern	Percentages (%)
Sudhamani S *et al.* [19]	2015	100	HMB	54
Mishra B *et al.* [17]	2017	400	HMB	51
Khan A *et al.* [16]	2017	300	HMB	45
Present study	2018	300	HMB	29

In the present study, heavy menstrual bleeding was the most common type of bleeding pattern observed in 86 (29%) of women. In other studies heavy menstrual bleeding is reported in 45-54% of patients [16, 17, 19].

In present study proliferative endometrium was observed in 42 % patients. The other studies have described proliferative phase endometrium in 27-61% patients [12-21]. In one study

proliferative phase was observed in 3% [21].

Secretory endometrium was the second most common histopathological finding identified in 48 women (16%).Reports from other studies have described secretory endometrium in 8-61% [12-20]. The bleeding in secretory phase is due to ovulatory dysfunctional uterine bleeding.

We have found atrophic endometrium in 17% patients and is the third common histopathological finding. Our studies have reported atrophic endometrium in 1 to 24% patients [13, 15, 18]. However endometrial atrophy is also a most common cause of bleeding in postmenopausal bleeding [12, 14, 18]. In most of the cases of AUB there is no specific organic cause as shown in various studies. In our study 75 % of women did not show any specific pathology for AUB.

Endometrial hyperplasia is a result of endogenous (chronic anovulation) or exogenous (hormone replacement therapy) prolonged estrogen stimulation.Clinically, endometrial hyperplasia manifests as heavy uterine bleeding. Endometrial hyperplasia with morphological and biological alterations of endometrial glands and stroma may precede or coexist with endometrial cancer [22].

Endometrial hyperplasia was another common finding observed in our study, it was seen in 13% of women having reproductive age group. In other studies endometrial hyperplasia was found in postmenopausal age group [12-18]. 4/40 women in our study showed atypical hyperplasia.

In the present study, endometritis was detected in 8% of the cases. Our incidence was higher than the studies reported by Singh N *et al*. % [15], Divya D *et al*. % [21], Gulia SP *et al*. % [12] and Shah RJ *et al*. % [20]. The possible explanation could be that most of patients in our region belong to rural and lower socioeconomic status and are living in unhygienic conditions with lack of awareness. In the present study, endometritis was most commonly seen in reproductive and perimenopausal age group, since these age groups have a greater chance of exposure to pelvic inflammatory disease due to prior instrumentation, spontaneous and therapeutic abortions, intra uterine contraceptive devices, ascending route of infection, etc. Hence are prone to develop endometritis.

Polyps are thought to be related in some way to hyperestrogenism.

In the present study, polyp were observed in only 4 (2%) cases and this was comparable with the study by Shah RJ *et al*. [20] In a study by Divya D *et al*. endometrial polyp was seen in 14% of women [21].

There has been a sizeable variation in the incidence of endometrial carcinoma reported by various studies over years. This could be attributed to the variation in the geographical location, differences in lifestyle, socioeconomic conditions, as also the difference in the inclusion criteria of various studies.

In the present study, endometrial carcinoma was observed in only 1 (0.5%) women. This was comparable with the study done by Shah RJ *et al*. (0.3%) [20], Gulia SP *et al*. (1%) [12], Vaidyea S *et al*. (1%) [13], Mishra B *et al*. (2%) [19] and Khan A *et al*. (2%) [16]. Our present study was endometrioid endometrial carcinoma (adenocarcinoma) presented with postmenopausal bleeding.

One of the patients in this study who presented with AUB had endometrial stromal sarcoma (0.50%). Similar finding was also noted in the studies done by Sajitha *et al*. [23] who reported one case of endometrial stromal sarcoma.

97/300 women in our study had leiomyoma or adenomyosis. The cause of AUB in these cases cannot be definitely concluded.

Most hysterectomies are performed for benign gynecological reasons such as fibroids, dysfunctional uterine bleeding, uterine prolapse. In India, hysterectomy has received increased attention in health policy debates in the past few years [24]. The trigger for increased focus is provided by a series of media reports that have highlighted an unusual surge in the number of women undergoing hysterectomy in many parts of the country, with a significant number of cases involving young and pre-menopausal women from poor families.[7] This rising number of young women undergoing hysterectomy has raised suspicions about unscrupulous practices on the part of health care providers. Thus, hysterectomy remains a matter of diverse debate owing to its physical, emotional, economic, sexual, and medical significance to women [25].

Conclusion

Though numerous medical treatment and conservative surgeries have emerged hysterectomy is the definitive treatment modality for AUB in the developing and the affluent countries.

All hysterectomy specimens even if it appears grossly normal should be subjected for histopathological examination regardless of the pre-operative diagnosis. Clinically unsuspected incidental findings can be found in hysterectomy specimens. It can inform us the exact cause of AUB.

However this study also gives a basic information and statistics to follow the trend of the hysterectomy and the corresponding histopathological findings in the studied population in a rural based tertiary care centre in western part of India**.**

We have classified the specimens according to PALMCOEIN and found out the percentages of each causes of AUB after excluding criteria from our study.

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