Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 04, pp.15176-15179, April, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

HISTOPATHOLOGY OF ENDOMETRIUM IN DYSFUNCTIONAL UTERINE BLEEDING –A REVIEW

[1]*Dr. Prasad Usha, [2]Dr. R. Vidyarama and [3]Dr. Prasad Uma

Andhra Medical College, Visakhapatnam, Andhra Pradesh, India

ARTICLE INFO

Article History:
Received 20th January, 2015
Received in revised form
19th February, 2015
Accepted 23rd March, 2015
Published online 30th April, 2015

Key words:

Dysfunctional uterine bleeding,
Endometrial histopathology.

ABSTRACT

Background: Dysfunctional uterine bleeding is a common problem in women accounting for one third of all gynaecological consultations carried out for abnormal uterine bleeding. The pathophysiology is not fully understood and complex. Specific diagnosis of functional disorder can be achieved by histopathological examination of the endometrium.
Aims: To study various patterns on histopathology in cases of dysfunctional uterine bleeding.
Material and methods: Consecutive endometrial curettings of 654 cases of dysfunctional uterine bleeding in the age group 20 to 60 years over a period of one year were included in the study. Organic lesions of the uterus were ruled out by ultrasonography. The tissue was routinely processed and stained with Hematoxylin and Eosin and the histological patterns were recorded.
Results: Out of 654 cases of dysfunctional uterine bleeding, 53.51% cases presented with anovulatory patterns and ovulatory patterns in 38.53%. Endometrial hyperplasia was seen in 7.64% of cases and granulosa cell tumor of ovary in 2 cases. Endometrial hyperplasia was more common in the age group beyond 30 years.
Conclusion: In cases of dysfunctional uterine bleeding a precise histological typing of lesions is very much essential in the management as it can predict the functional disorder by looking at the morphology of the glands and the stroma.

INTRODUCTION

Uterine bleeding is designated abnormal if it is excessive or scant or if occurs at the wrong time. The causes of bleeding could be due to focal abnormalities in the uterine corpus or dysfunctional uterine bleeding (DUB) where there is no visible abnormality in the corpus. The causes of dysfunctional uterine bleeding is usually related to one of the three hormonal imbalances a) estrogen breakthrough bleeding, b) estrogen withdrawal bleeding and c) progesterone breakthrough bleeding. Estrogen breakthrough withdrawal bleeding occurs when excess estrogen stimulates the endometrium to proliferate in undifferentiated manner with insufficient progesterone to provide structural support, portions of endometrial lining slough at irregular intervals. The usual progesterone guided vasoconstriction and platelet plugging do not take place often resulting in profuse bleeding. Estrogen withdrawal bleeding results due to sudden decrease in estrogen levels. Histopathology shows disparity between the endometrial patterns observed and that expected from the time of cycle. The maturity of the endometrial glands lags behind. Stromal crumbling with presence of fibrin, thrombi and apoptotic bodies at the base of the glands is seen (Kathleen, 1999). The present study is conducted at a tertiary care centre which caters to the need of semiurban, rural and tribal population, who cannot afford costly investigations like hormone estimations; hence histopathology of the endometrium is the cheapest way to determine the functional disturbances.

Corresponding author: Dr.Prasad usha
Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.

MATERIALS AND METHODS

Consecutive 654 cases of dysfunctional uterine bleeding in the age group 20 to 60 years undergoing endometrial biopsy at our hospital, over a period of one year were included in the study. The organic abnormalities were ruled out by ultrasonography. The cases with inadequate yield of biopsy and those showing products of conception on histopathology were excluded from the study. The biopsy material was fixed in 10% formalin and the sections were stained with hematoxylin and eosin. Histopathological examination of the endometrial biopsies was done and the various patterns were recorded.

RESULTS

In the present study out of 654 cases of dysfunctional uterine bleeding, 350/654(53.51%) cases showed anovulatory patterns and ovulatory patterns in 252/654 (38.53%). Histopathological patterns of anovulatory cycles were: atrophy (120/350, 34.28%), deficient proliferation (50/350,14.28%), irregular proliferation (110/350,31.42%) and disorderly proliferative endometrium in (70/350, 20%). Histopathological patterns of ovulatory cycles were: deficient secretory phase in (56/252, 22.22%) with deficient secretory dissociated delay in

(20/56,35.71%) and deficient secretory phase with co-ordinated delay in (36/56,64.28%) Irregular shedding was seen in 140/252(55.55%) of cases. Endometrial hyperplasia was seen in 50/654(7. 64%) of cases and granulosa cell tumor of ovary in 2 cases (0.30%) (Table 1).

Table 1. Various Histological Patterns of Dysfunctional Uterine Bleeding - 654

Histological patterns	Number of cases	Percentage
ANOVULATORY PATTERNS	350	53.51
Atrophy	120	34.28
Deficient proliferation	50	14.28
Irregular proliferation	110	31.42
Disorderly proliferative	70	20
OVULATORY PATTERNS	252	38.53
Deficient secretory phase	56	22.22
Deficient secretory phase with dissociated delay	20	7.93
Deficient secretory phase with co-ordinated delay	36	14.28
Irregular shedding	140	55.55
OTHERS	52	7.95
ENDOMETRIAL HYPERPLASIA	50	
Simple hyperplasia without atypia	44	88
Complex hyperplasia without atypia	4	08
Complex hyperplasia with atypia	2	04
GRANULOSA CELL TUMOR OF OVARY	2	3.84

Anovulatory cycles were more common in the age group 31-40 years (175/654,26.75%) followed by ovulatory cycles (143/654,21.86%). Endometrial hyperplasia was more common in the age group beyond 30 years with maximum number of cases in the age group 41-50 years(25/50,50%). (Table 2)

Table 2. Age Distribution of Various Patterns: 654

Histological patterns	Number of cases	21-30 years	31-40 years	41-50 years	51-60 years
Anovulatory patterns	350	70	175	98	7
Ovulatory patterns	252	53	143	56	-
Simple hyperplasia without atypia	44	1	17	22	4
Complex hyperplasia without atypia	4	-	-	3	1
Complex hyperplasia with atypia	2	-	-	-	2
Granulosa cell tumor of ovary	2	-	-	-	2

DISCUSSION

Primary vascular alterations are found in hyperestrogenic type endometrium i.e anovulatory DUB and progestational type of endometrium. It is initiated by either micro erosions or vascular fragility due to structural abnormalities of microvessels. Of all the target organs for ovarian hormones, the endometrium is the most sensitive. It is vital for the normal development of the endometrium that the opposing hormones, estrogen and progesterone remain in physiological balance. Altered ovarian function may be either primary due to intrinsic ovarian disease or secondary due to disturbance in the hypothalamic-pituitary axis. Since different functional disorders can cause the same kind of hormonal imbalance, they also can induce the same structural change of the endometrium. Specific diagnosis of functional disorder can be achieved by histopathological examination.

Anovulatory disturbances

Atrophic Endometrium and weakly proliferative Endometrium (Deficient Endometrium)

Endometrial atrophy is normal for both postmenopausal and prepubertal girls. During the reproductive years, it is always abnormal and indicates a complete lack of endometrial response to hormones. Atrophic and deficient endometrium are defined as those deprived of functionalis and consisting of exclusive of thin basalis with few narrow tubular glands., lined by cuboidal indeterminate epithelium, showing neither proliferative nor secretory activity. A frequent variant of this structure, tubular atrophy was an atrophic end with cystically dilated glands lined by flattened to indeterminate type of epithelium-cystic atrophy. Atrophic or deficient proliferative endometrium are defined by the following criteria a) shallow endometrium 2.2mm thick, with loss of distinction between the basal and functionalis layer. b) proliferative type of endoglands, somewhat tortuous, with tall columnar pseudostratified epithelium, oval nuclei and very infrequent mitosis with dense fibrotic stroma, devoid of mitosis.c) mixed forms of endometrial tissue both atrophic and weakly proliferative glands (Archer, 1991). Atrophic endometrium is one of the commonest causes of post menopausal bleeding. Uterine atrophy is a condition that is caused by low levels of estrogen. It causes the walls in the uterus to become thin, making the uterine blood vessels weak and susceptible to spontaneous bleeding. (Ferrazzi *et al*., 1996) in their study analysed 930 patients with post menopausal bleeding. The prevalence of atrophy was 49.2% and endometrial thickness on sonography ≤ 4mm safely predicted endometrial atrophy. (Damle *et al.,* 2013) reported atrophic endometrium in 25.80% of cases with post menopausal bleeding. (CHOH *et al*., 2013) reported atrophic endometrium in 32.7% of cases with post menopausal bleeding. (Pankaj Malukani *et al.,* 2013) in their study the commonest pattern seen on histopathology in cases of DUB were proliferative pattern in 39.75% of cases and atrophic pattern in 7% of cases. (Narula *et al*., 1967) documented 37.77% proliferative endometrium and 5.46% atrophic endometrium. Sanaullah *et al.* (2004) reported proliferative endometrium in 31% of cases. In the present study atrophic endometrium was seen in 34.28% of cases and deficient proliferative endometrium in 14.28% of cases.

Irregular proliferation and Disorderly proliferative endometrium

Although the follicle has normally matured, ovulation may take place, either because of a central defect in LH stimulation or hyperstimulation with FSH or because of ovarian damage. The unruptured (persistent) follicle will continue to produce estrogen beyond the proliferation phase for a varying number of days and will then slowly regress, resulting in anovulatory shedding which may occur at the same time as menstrual shedding. Irregular proliferation may also develop when previous repeated anovulatory cycles have built up a relative estrogen predominance which increased with each successive anovulatory cycle.Histologically the growth of the glands and stroma clearly excess that of the normal proliferative phase. The glands vary in their distribution, lying either closely packed or widely dispersed with variable diameter. Some of them lined by pseudostratified epithelium or even stratified high columnar epithelium. In disorderly proliferative endometrium there is absence of uniform glandular development due to dys synchronous growth of the functionalis. The glands may be cystically dilated show budding metaplastic epithelium with absence of cytological atypia. The glands to stroma ratio is normal. This is a normal pattern seen in perimenarchial and post menopausal period. In

the study by Vaidya *et al* 2013 showed disorderly proliferative endometrium in 13.40% of cases.In study by Jetley *et al.* 2013 analyzed 219 cases with perimenopausal bleeding in which disorderly proliferative endometrium in 6.8% of cases. In the study by Soleymani *et al.* 2013 disorderly proliferative endometrium was seen in 15.40% of cases. In the study by Doraiswami *et al.* 2011 the disorderly proliferative endometrium was seen in 20.5% of cases. In the present study irregular proliferative endometrium was seen in 31.42% cases with premenopausal bleeding and disorderly proliferative endometrium in 20% of cases with perimenopausal bleeding.

Ovulatory disturbances

Defecient secretory phase

Encompasses a variety of disturbances in corpus luteum function of central or ovarian origin with or without preceding abnormal follicular development. The shedding of endometrium takes place prematurely because levels of progesterone decline due to abnormal corpus luteum. The endometrial pattern in co-ordinated apparent delay on histopathology there are partly dilated glands with beginning of secretion on 26th day of menstrual cycle, in deficient secretory phase with co-ordinated true delay the narrow straight glands show beginning secretion at the 25th day of cycle. In the present study deficient secretory phase was seen in 22.22% of cases with dissociated delay in 7.93 cases and co-ordinated delay in 14.28% of cases.

Irregular shedding

If the normally developed corpus luteum fails to regress at the correct time and consequently continues to secrete progesterone then the menstrual bleeding will be prolonged and sometimes delayed. On histology there is diverse admixture of endometrial fragments in various stages of regression and dissociation still evident several days after menstruation started. The normally developed endometrium cannot disintegrate; it merely shrinks owing to the loss of water induced by the decrease in estrogen. Since the shedding is greatly prolonged the regressive changes in the glands and stroma become more intense and more striking than those normally seen before and during a regular menstruation. Due to protracted regression and shrinkage the glandular lumina become characteristically star shaped. The cytoplasm of many of the glands is clear. The nuclei may be small or large, pleomorphic and hyperchromatic. The stroma consists of densely packed predecidual cells and endometrial granulocytes. In the present study irregular shedding was seen in 55.55% of ovulatory disturbances. **(**Pankaj Malukani *et al* ., 2013) in their study the secretory pattern was seen in 31.25% of cases. (Narula *et al.,* 1967) documented 35.95% secretory endometrium and (Sanaullah *et al.,* 2004) reported secretory endometrium in 43% of cases of DUB.

Endometrial hyperplasia

Failure to ovulate, after menopause first deprives the endometrium of progesterone stimulation. The estrogen stimulation, however may continue because of conversion of androgen secreted by menopausal ovaries and adrenal cortices into estrogens. Obesity, diabetes and other metabolic disorders may enhance the extragonadal endogenous estrogen production by aromatisation. High estrogen levels, especially estradiol, are often associated with endometrial hyperplasia, because of binding of the hormone to receptor sites in the nuclei of endometrial cells. The response of the endometrial tissue to a continuous, prolonged and unopposed(by progesterone) estrogenic stimulation in post menopausal women lead to hyperplastic endometrium and possibly neoplasia (Gurpide, 1977).

On histopathology hyperplasia denotes proliferating endometrium featuring glandular architectural abnormalities that result in glandular crowding and take the form of simple hyperplasia or complex hyperplasia. Simple hyperplasia with atypia show cystically dilated glands and minimal budding glands that are seperated by wisps of compressed stroma. The lining epithelium is proliferative and comparable to normal late proliferative phase with nuclear atypia, if absent then it is simple hyperplasia without atypia. In complex hyperplasia without atypia there is increase in the number and size of endometrial glands, marked gland crowding and branching of glands. However, the glands remain distinct and non confluent and the epithelial cells remain cytologically normal. In complex hyperplasia with atypia the architectural features are similar to complex hyperplasia without atypia but the nuclei show atypia with prominent nucleoli and in 23% to 48% there is chance of associated malignancy. In postmenopausal patients with atypical bleeding,transvaginal sonographic measurement of endometrial thickness (> 4mm),integrated with individual risk factors,can help in the diagnosis of endometrial carcinoma (Ferenczy and Gelfand, 1989; Archer, 1991).

In study by Vaidya *et al.* 2013 endometrial hyperplasia was seen in 10.9% of cases and more common in peri and postmenopausal period. In study by Jetley *et al.* 2013 endometrial hyperplasia was seen in 10.9% of total cases, simple hyperplasia without atypia in 79.1%, complex hyperplasia without atypia in 16.66% and complex hyperplasia with atypia in 4.16% of cases. In study by Soleymani *et al* 2013 endometrial hyperplasia was seen in 2.5% of cases. In study by Doraiswami *et al.* 2011endometrial hyperplasia was seen in 6.1% of cases. In study by Damle *et al.* 2013 out of 119 cases above 40 years, endometrial hyperplasia was seen in 19.35% of cases and presented with post menopausal bleeding. In study by Cho *et al* 2013 endometrial hyperplasia was seen in 10.4% of cases. Pankaj Malukani *et al.* 2013 in their study endometrial hyperplasia was seen in 22% of cases. Narula *et al.* 1967 documented 20.90% endometrial hyperplasia and Sanaullah *et al.* 2004 reported endometrial hyperplasia in 11% of cases of DUB. Zawar *et al.* 2005 reported endometrial hyperplasia in 21.14% and Pilli *et al* 2002 reported endometrial hyperplasia in 44% of cases. In the present study endometrial hyperplasia was seen in 7.64% of cases presenting with post and perimenopausal bleeding.

Conclusion

Dysfunctional uterine bleeding is the commonest presenting symptom in gynecology outpatient department. Endometrial sampling and histopathology could be effectively used as the first diagnostic step in dysfunctional uterine bleeding.

Anovulatory patterns are more common in the pre and peri menopausal group. Atrophic endometrium and endometrial hyperplasia was commonly associated with post and perimenopausal bleeding. Disorderely proliferative endometrium was associated with perimenopausal bleeding.

REFERENCES

Archer, D. F., M. C. Intyre, Seiltman, K., Wilborn, W. W. et al. 1991.Endometrial morphology in asymptomatic post menopausal woman. *Am J Obstet Gynecol*., 165; 317-22.

Cho, H. J., Lee, E. S., Lee, J. Y., Hong, S. N., JIYI, Kim, H. Y. and Kim A. 2013.Investigations for postmenopausal uterine bleeding:Special consideration for endometrial volume.Arch Iran Med.,16(11):665-70.

Damle, R. P., Dravid, N. V., Suryawanshi, K. H., Gadre, A. S., Bagale, P. S. and Ahire, N. 2013. Clinicopathological spectrum of endometrial changes in perimenopausal and postmenopausal Abnormal uterine bleeding: A 2 year study. *J Clin Diagn Res*., 7 (12):2774-6.

Doraiswami, S., Johnson, T., Rao, S., Rajkumar, A., Vijaya Raghavan, J., Panicker, V. K. 2011. Study of endometrial pathology in abnormal uterine bleeding.J Obstet Gynaecol India., 61(4):426-30.

Ferenczy, A. and Gelfand, M. 1989.The biologic significance of cytologic atypia in progesterone treated endometrial hyperplasia. Am J Obstet Gynecol., 160:126.

Ferrazi, E.,Torvi, V., Trio, D., Zannoni, E., Filiberto, S, Dordoni, D. 1996.Sonographic endometrial thickness a useful test to predict atrophy in patients with premenopausal bleeding – An Italian Multicenter study. Ultrasound Obstet Gynecol., 7(5):315-21.

Gurpide, E. T., Seng, L. and Guoberg, S. B. 1977.Estrogen metabolism in normal and neoplastic endometrium. *Am J Obstet Gynecol*.,129:809-16.

Jetley, S., Rana, S., Jairajpuri, Z. S. 2013. Morphological spectrum of endometrial pathology in middle aged women with atypical uterine bleeding: A study of 219 cases. *J Midlife Health.,* 4(4):216-20.

Kathleen, A., Oriel, Sarina Schrager.Abnormal uterine bleeding1999. *Am Fam Physician*., 60(5):1371-1380.

Narula. R. K. 1967. Endometrial histopathology in DUB. *Journal of Obstetric and Gynaecology of India*., 17:14-18.

Pankaj Malukani, R. N. Gonsai, Richa Sharma, Hemina Desai, H. M. Goswami, Nirav Hingrajia. 2013.Histo-Pathological study of Endometrium in Dysfunctional Uterine Bleeding-a study of 400 cases.SEAJCRR.,2(6):429-435

Pilli, G. S., Sethi, B. and Dhaded, A. V. 2002.Dysfunctional uterine bleeding (study of 100 cases). *J Obstet Gynecol India.,* 52(3):87-9.

Sanaullah Gazozai, Qurban Ali, Bugti, Ayesha Siddique, Naila Ehsan. 2004. Excessive uterine haemorrhage-A Histopathological study. *Gomal Journal of Medical Sciences.,* 2(1):13-15.

Soleymani, E., Ziari, K., Rahmani, O., Dadpay, M., Taheri-Dolata badi M., Alizadeh, K., Ghanbazadeh, N. 2013. Histopathological findings of endometrial specimen in abnormal uterine bleeding. Arch,Gynecol Obstet.

Vaidya, S., Lakhey, M., Vaidya, S., Sharma, P. K., Hirachand, S.. Lama, S., KCS. 2013 Histopathological pattern of abnormal uterine bleeding in endometrial biopsies. *Nepal Med Coll J.,* 15(1):74-7.

Zawar, M. P. Bolde, S., Rathi. 2005. Histopathology study of endometrium in dysfunctional uterine bleeding. *Solapur Medical Journal*., 14

****