



Case Report

Exogenous Hormone Induced Abnormal Uterine Bleeding-A Case Report

Authors

P. Divya¹, M.Mounika², K. Lavanyakumari³, Rehana Tippoo⁴, P. Viswanathan⁵

^{1,2}Post graduate in Pathology, ³Professor and Head in Obstetrics and Gynaecology

^{4,5}Professor in Pathology

Department of Pathology, Rajah Muthiah Medical College and Hospital, Annamalai University,
Annamalainagar, Chidambaram- 608002

Corresponding Author

P. Viswanathan

Professor in Pathology, Department of Pathology, Rajah Muthiah Medical College and Hospital, Annamalai
University, Annamalainagar, Chidambaram- 608002, India

Email: drpviswanathan2014@gmail.com, Mob: 9865038041

Abstract

A 40-year-old lady with a history of Abnormal Uterine Bleeding (AUB) was prescribed Ormeloxifene, at a dosage of 60 mg once in 3 days for a period of 3 months following a fractional curettage. Subsequently the patient had taken hormonal analogues over a long period of time without a proper follow up. Later due to a persistent and intermittent Abnormal Uterine Bleeding (AUB), she approached the hospital again and a planned hysterectomy was done. The hysterectomy specimen exhibited simple endometrial hyperplasia with focal sessile endometrial polyps. The myometrium was hypertrophic and hyperplastic in nature, simulating the pregnancy changes with multiple foci of adenomyosis (florid adenomyosis). The right side fallopian tube also showed endometriosis. This case is being presented to stress the fact that whenever a patient is under a hormonal therapy for AUB, proper follow up should be done to look for endometrial changes via noninvasive ultrasonography and if any unusual findings are found, an endometrial biopsy should be done to rule out any changes.

Keywords: Ormeloxifene, Pregnancy changes, Endometrial polyp, Endometrial hyperplasia, Florid adenomyosis, Endometriosis of Right Fallopian tube.

Introduction

Abnormal uterine bleeding (AUB) is generally managed by exogenous hormones or hormonal analogues. The present concept is to manipulate the receptors to suit the clinical need. A fourth-generation drug in this area is Ormeloxifene (Centchroman) which is one of the selective oestrogen receptor modulators. The chemical

name of Ormeloxifene is trans-7-methoxy-2,2-dimethyl-3-phenyl-4-(4-2-pyrrolidinoethoxy) phenyl-chromanhydrochloride). Ormeloxifene is best known as a non-hormonal, non-steroidal oral contraceptive taken once a week. Available since 1990s, the drug is marketed as Centchroman. The drug is anti-estrogenic as well as anti-progesterone in action and is used as a non-hormonal oral

contraceptive. As contraceptives, the tablets are dispensed as 30 mg of Centchroman in each bubble of a strip with 30 slots. 21 slots as the dated drugs and the remaining slots contain Iron supplements.

The action of the drug is prevention of proliferation and decidualisation of the endometrium, enhanced blastocyst formation and slightly increased rate of embryo transport through the oviducts. Ormeloxifene is also approved for treatment of dysfunctional uterine bleeding associated with an ovular cycle occurring near menopause. Ormeloxifene competitively binds with cytosol receptors and blocks them to cause prolonged depletion of hormonal action which lasts longer even after withdrawal of the drug. Ormeloxifene a Selective Estrogen Receptor like Modulator acts on the endometrium resulting in epithelial multilayering, can induce proliferative activity or hyperplasia in women receiving treatment for breast cancer. Ormeloxifene selectively bind with high affinity to estrogen receptors (ER) and mimics the effect of estrogen in vagina, bone, cardiovascular system and central nervous system but acts as estrogen antagonist in uterine and breast tissue. The drug is therefore, suitable in the treatment of heavy menstrual bleeding (AUB).

The unmonitored intake of this drug can lead to several complications like bagginess of breast. Endometrium of such patients may exhibit variety of appearances including hyperplasia following therapy.

Endometrial hyperplasia (EH) has a high risk for malignant transformation and persistence of EH is caused by continuous exposure to estrogen unopposed by progesterone similar to polycystic ovary syndrome. The treatment can result in the endometrial hyperplasia which can progress, or often occur coincidentally with endometrial carcinoma.

Case Presentation

A 40-year-old lady presented with complaint of pain over the right side of the lower abdomen for

about a week with excessive bleeding during menstruation in the recent past, with minimal spotting on and off. Three years back before the present hospital visit, she had one episode of prolonged menstrual bleeding for 3 months, a diagnostic dilatation and curettage was done, which showed -Irregular proliferative pattern. Subsequently, the patient was started on Ormeloxifene 60 mg once in 3 days for a period of 3 months. She didn't come for follow-up after this treatment. Patient now underwent hysterectomy for excessive bleeding. Post operatively the specimen was sent for histopathological examination. Grossly the specimen showed endometrial cavity which almost obliterated with endometrial hyperplasia and multiple sessile endometrial polyps along with areas of hemorrhage. The endometrium was friable in nature. Myometrium appeared hyperplastic in nature with focal areas of hemorrhage. Adequate sampling was done and subsequently microscopic examination was done where the endometrial glands were of varying sizes and shapes. Most of them were tubular and rounded in configuration. All the endometrial glands are lined by single layer of low columnar cells without any stratification or pseudo stratification. Some of the glands were cystically dilated. Few glands exhibited stellate configuration. The gland to stroma ratio was not significantly altered. Stroma is edematous in nature. At places the endometrial tissue appeared like a polyp. The vessels are dilated and congested. There are areas of hemorrhage. Corpus Uterus revealed hyperplasia and hypertrophy of the uterine musculature (simulating pregnancy changes). Right ovary showed thickening of cortex and stroma simulating hyperthecosis and with the presence of corpus albicans. Left Ovary showed a cyst lined by benign low cuboidal to columnar cells. The cyst is filled with gelatinous material (simple cyst). Stroma had congested blood vessels and corpus albicans was present. Right fallopian tube exhibited endometriosis. Sections from left side fallopian tube exhibited hematosalpinx. The

uterine cervix exhibited chronic non-specific cervicitis.

A final diagnosis was made as simple hyperplasia of the endometrium with focal sessile endometrial polyp with myohyperplasia, hypertrophy, florid adenomyosis of uterus, endometriosis of right side fallopian tube and chronic non-specific cervicitis.



Figure: 1



Figure: 2 Body Shows Hyperplasia and Hypertrophy Simulating Pregnancy Changes of Uterus. Endometrial Cavity is Filled with Black Coloured Friable Material. Cervix is Folded Over the Body.

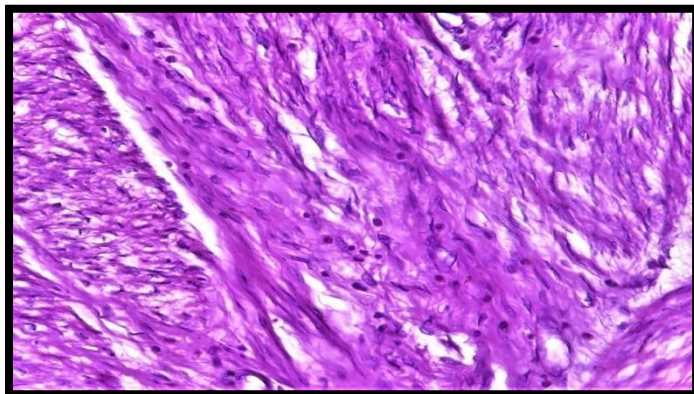


Figure: 3 Myohyperplasia and Myohypertrophy

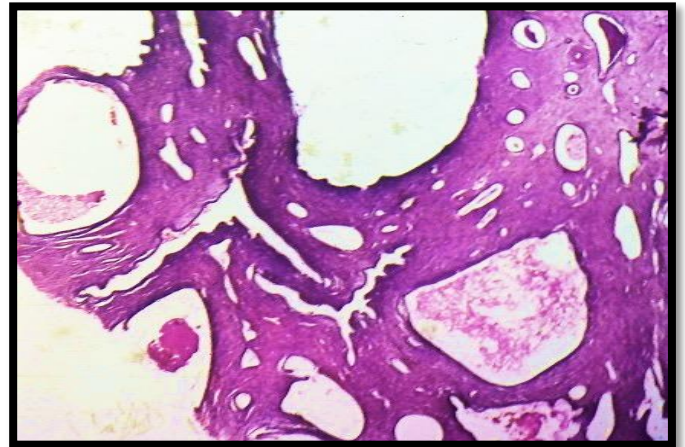


Figure: 4- Adenomyosis in the Body

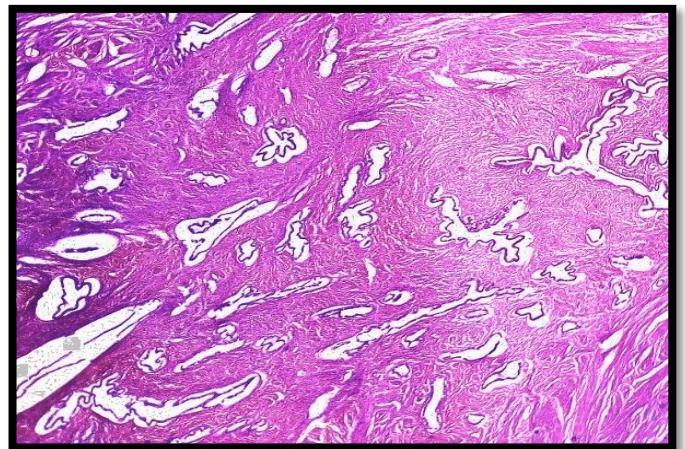


Figure: 5

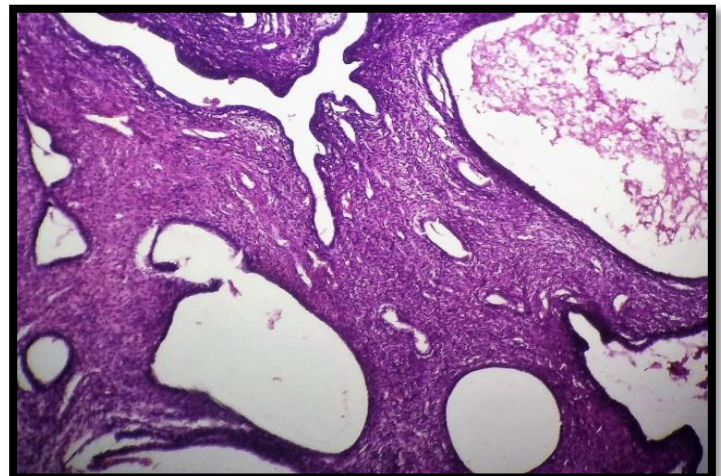


Figure: 6- Endometrial Polyp

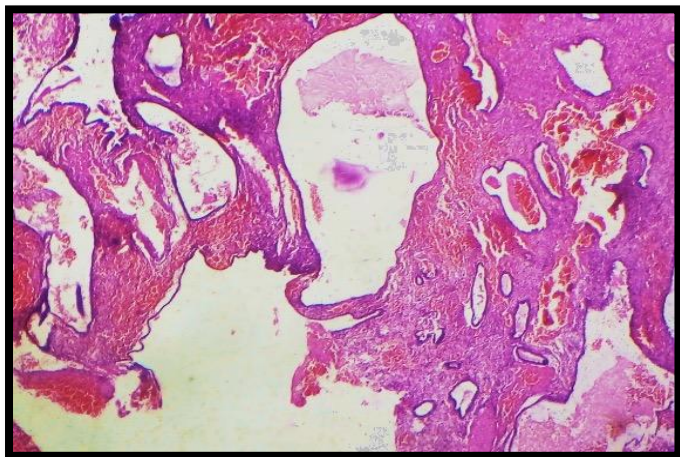


Figure: 7

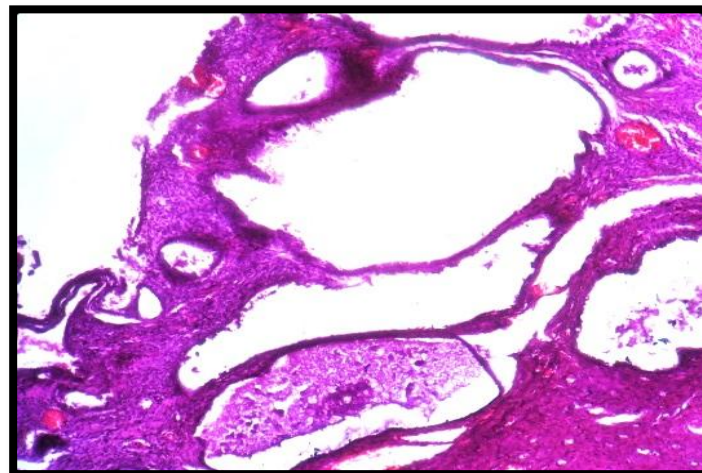


Figure: 11 10x- Endometrial Glands Are of Varying Sizes and Shapes. Presence of A Polyp where Some of the Glands Are Cystically Dilated and Lined by Single Layer of Columnar Cells. Some of the Glands Contain Secretions

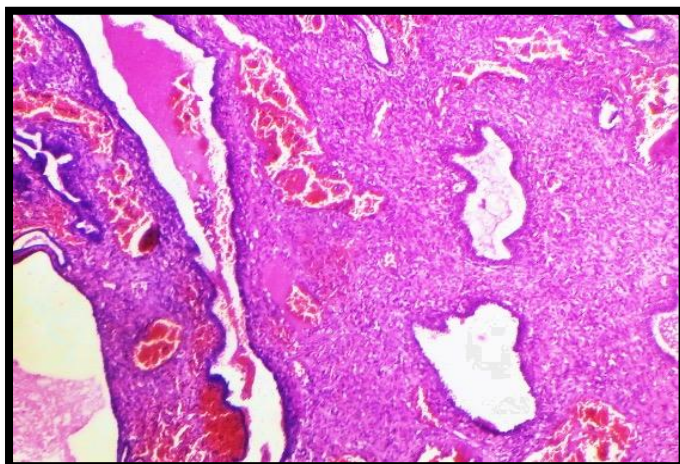


Figure: 8 Another Area of Polyp Depicting Areas of Hemorrhage and Dilated Congested Blood Vessels, which may be the Reason for Persistent AUB.



Figure: 12- 1X

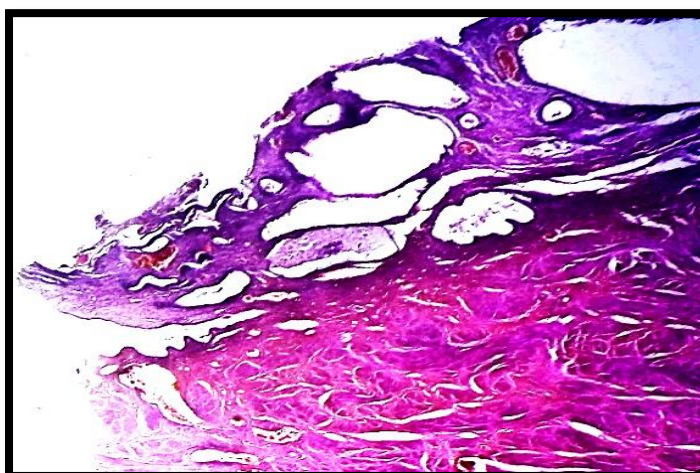


Figure: 9- 4X

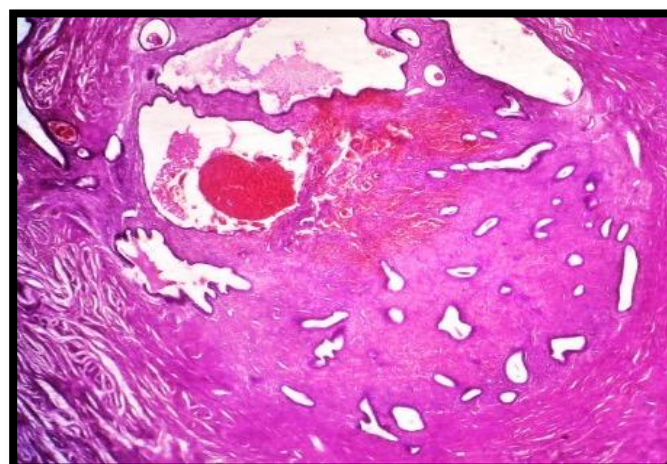


Figure: 13- 4X

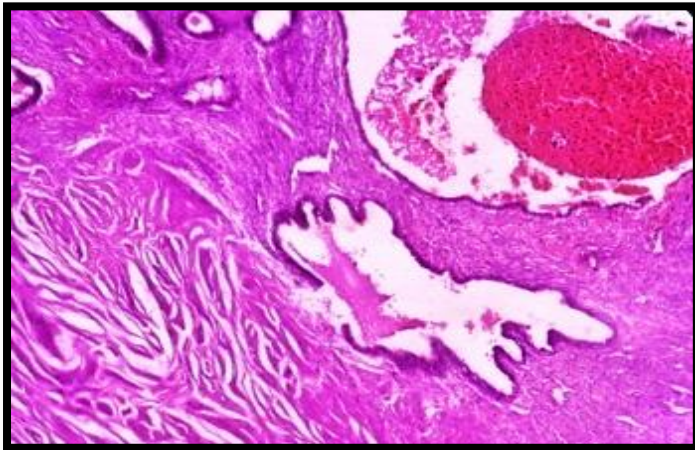


Figure: 14- 10x- Right Fallopian Tube shows Endometriosis

Discussion

Hormones and hormonal analogues are routinely used in the clinical practice for various reasons, e.g. contraception, acne treatment and hormone replacement therapy. They are also used to manage Abnormal Uterine Bleeding, as well as an adjuvant in treatment of Hormone responsive malignant tumors.

Abnormal uterine bleeding (AUB), which is defined as excessively heavy, prolonged and/or frequent bleeding of uterine origin. Dysfunctional uterine bleeding (DUB), which is characterizing any AUB when all possible underlying pathologic causes have been previously excluded.

Effect of Estrogen on Endometrium

In normal circumstances, estrogens cause growth of the glands, stroma and vasculature of endometrium and also the induction of progesterone receptors in the endometrium. If estrogens are started early in normal proliferative phase, endometrial growth is prolonged and the endometrium exhibits features of a prolonged proliferative pattern, the ovulation is suppressed due to gonadotropin inhibition and the secretory phase is delayed or absent. Following ovulation, there is edema in the mid-secretory phase along with growth of spiral arteries in the late secretory phase which is followed by differentiation due to progesterone.

Effect of Progesterone on Endometrium

Progesterone is responsible for cellular differentiation in the endometrium and inhibits the effects of estrogens. When given in proliferative phase, ovarian follicular development is depressed, ovulation is postponed and endometrium growth ceases. Prolonged use produces atrophic endometrium. It shows sparse, uncoiled glands set in a shallow, compact, weak pseudodecidualized stroma.

Conclusion

Whenever hormones are prescribed to any patient, the patient need to be followed up very regularly in a scheduled way. The follow up should involve not only clinical examination and ultrasonography observation but also might require endometrial biopsy to exclude the possibility of pseudo pregnancy changes, polypoidal hyperplasia or any carcinomatous changes. A 40-year-old lady who was on hormones without proper monitoring for 3 years, landed up with persistent bleeding with benign endometrial hyperplasia and pregnancy like changes. The case is being reported to highlight the effects of the hormonal therapy.

Sources of Support in the form of Grants- Nil

References

1. Kumaran RJ, Mazur MT: Benign diseases of the endometrium. In Kumaran RJ(ed):Blaustein's Pathology of the Female Genital Tract,5thed.New York, Springer-Verlag,1995,pp 367-409.
2. Charles D:Iatrogenic endometrial patterns. J Clin Pathol 17:205,1964
3. Floyd WS: Danazol: Endocrine and endometrial effects. Int J Fertil 25:75-80,1980.
4. Garcia JE, Acosta AA, Hsiu JG: Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin /human chorionic gonadotropin for in vitro fertilization. Fertil Steril 41:31-35,1984

5. Laurence Bruton, Bjorn Knollman, Randa Hilal- Dandan: The Pharmacological Basis of Therapeutics,13th ed. Goodman & Gilman's, 2017,pp 827-830
6. Croxatto HD, Diaz S,Pavez M: The endometrium during continuous use of Levonorgestrel. In Zatuchini GI, Goldsmith A, Sheldon JD, Sciarra JJ(eds): Long Acting Contraceptive Delivery Systems. Philadelphia, Harper & Row, 1984p 290.