Abnormal uterine bleed – An adverse event of long term centchroman use?

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Centchroman (levormeloxifene) is a synthetic non-steroidal compound used as an oral contraceptive. It is commonly believed to cause no hormonal imbalance with minimal side effects.
Abnormal uterine bleed – An adverse event of long term centchroman use?

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ABSTRACT

Background: Centchroman (levormeloxifene) is a synthetic non-steroidal compound used as an oral contraceptive. It is commonly believed to cause no hormonal imbalance with minimal side effects. Case: A 37 year old woman using centchroman for 10 years in an unsupervised fashion presented with abnormal uterine bleed and enlarged uterus of 18 week size. Malignancy was suspected clinicoradiologically and on fractional curettage. The histopathology of hysterectomy showed extensive decidual changes in a hyperplastic endometrium, and diffuse microglandular cervical hyperplasia. Conclusion: The case suggests a possible prominent hormonal effect of centchroman on the uterus. This could be a significant adverse event related to prolonged therapy.

Key words: centchroman; abnormal uterine bleeding; levormeloxifene

INTRODUCTION

Centchroman is a novel non-steroidal agent unrelated to any conventionally used contraceptive. This is the only anti-implantation agent approved for clinical use in the world. It offers a unique combination of weak estrogenic and potent antiestrogenic properties. The contraceptive effect is readily reversible and subsequent pregnancy and its outcome is normal. It scores over steroidal contraceptive pills because it does not disturb the endocrine system and the normal ovulatory cycle is maintained. However the long term unregulated use may be of concern.

CASE REPORT

A para 3, 37 year old woman presented with severe anaemia and meno-metrorrhagia for 2 years. There was history of continuous bleeding per vaginum with passage of clots for 1½ months. Initial menstrual cycles prior to 2 years lasted 10-15 days and came at an interval of 2-3 months. There was occasional dysmenorrhoea and dyspareunia. No history of contact bleeding was present. She further reported a contraceptive history of using centchroman (levormeloxifene) for 10 years in an unsupervised and irregular manner. On direct questioning, she recalled to have taken one tablet (30mg) of centchroman initially weekly for 3 months only.

On examination, she had subumbilical abdominopelvic midline mass upto 16 weeks size uterus. There was no organomegaly and no free fluid on abdominal palpation. Per speculum examination showed cervix to be hypertrophied with bleeding seen through os. Pervaginum, her uterus was enlarged uniformly upto 18 weeks size, hard in consistency with restricted mobility. The fornices were free.
All haematological investigations were normal except severe degree of anemia (hemoglobin 4.5 gms%). Urine pregnancy test was negative, serum β-HCG and thyroid stimulating hormone levels were normal. Her chest X-ray was normal and pap smear showed inflammatory pathology. Trans-vaginal sonography was suggestive of mixed echogenic collection (heterogenous myometrial echogenicity) in a distorted endometrial cavity of the bulky uterus (101x84mm) with normal ovaries. Doppler had no evidence of increased flow. On MRI, there was thickened endometrial canal (129x56mm) appearing heterogeneously hyperintense on T1/T2 weighted images (Figure 1). Myometrium and bilateral ovaries were normal. There was no lymphadenopathy or free fluid on imaging. Bladder and bowel loops were normal.

She received 5 units of blood transfusion for severe anaemia. Provisional clinical diagnosis of anemia with abnormal uterine bleeding, AUB (metropathia type) was made. However, her bleeding did not respond to medications (norethisterone acetate and tranexamic acid). Following failure of norethisterone therapy, surgical curettage was done. Uterocervical length was 12 cm. Histopathology of surgical curettage was hyperplasia of endometrium along with endocervical microglandular hyperplasia with atypia (Figure 2).
Failure of medical treatment for control of bleeding and atypia (?malignancy) prompted an early hysterectomy. On cut specimen, the uterus showed a grossly dilated uterine cavity completely obliterated by a fleshy endometrial growth, well delineated from the myometrium. The endocervical canal was diffusely involved by multiple nodular polypoidal growths (Figure 3). Bilateral tubes and ovary were normal. Histopathology showed extensive decidual changes in a hyperplastic endometrium and diffuse microglandular cervical hyperplasia (Figure 4). On retrospection, in view of absence of other medical causes, the hyperplasia of endometrium was attributed to possible exaggerated hormonal effect of
exogenous unregulated centchroman use for 10 years. The patient made an uneventful recovery post surgery.

Fig. 4: Endometrial glands in a decidualised stroma. Haematoxylin and eosin, 200x

DISCUSSION

Levormeloxifene (Centchroman) is a selective estrogen receptor modulator (SERM). Levormeloxifene has the unique distinction of being non-steroidal, no short term side effects like nausea, vomiting, weight gain, no adverse effect on lipid profile and platelet function as seen with steroidal contraceptives, easy dosage (twice a week on fixed days for the first three months, followed by one pill in a week thereafter) and affordable.\(^1\)

Usually well tolerated, common adverse effects reported with levormeloxifene are headache, abdominal pain and leukorrhea even after the highest daily dose of 160 mg.\(^3\)

Generally considered to be a safe drug, its prolonged use is often unmonitored in developing countries. Besides an oral contraceptive, levormeloxifene has been extensively studied for its potential use in prevention of bone loss and improving lipid profile, but the safety profile of levormeloxifene in postmenopausal women has raised concerns.\(^4\)

In a 2-year, multicenter, double-blind, placebo controlled study of the effect of levormeloxifene on 301 healthy postmenopausal women in the daily dose range of 1.25-40 mg, levormeloxifene decreased low density lipoprotein cholesterol by about 22-30% compared with about 12% in the low dose hormonal therapy (HT) group.\(^4\) Spinal bone mineral density (BMD) decreased by less than 1% in the placebo group and increased by about 2% in the levormeloxifene groups and by almost 5% in the HT group. This study provided evidence that levormeloxifene has estrogen-like effect on endometrium. Endometrial thickness increased
both clinically and statistically significantly in the levormeloxifene group independently of the dose; the difference from the placebo and HRT groups was significant (P < 0.001).\(^5\) The increase in endometrial thickness was believed to be related to focal and general fluid accumulation in the uterus.

A multicentered prospective study in 2924 postmenopausal women was halted after 10 months because of the large number of gynecologic and other adverse events observed due to levormeloxifene.\(^6\) A statistically significant increase rate of complication viz. leukorrhea, increased endometrial thickness on ultrasound scan (19%), enlarged uterus (17%), uterovaginal prolapse, urinary incontinence, increased micturition frequency, lower abdominal pain, hot flushes, and leg cramps were reported when compared with placebo.\(^6\)

Another study reported follow-up on the adverse events in a group of 234 women that were followed for 12 months without treatment after 12 months of treatment with levormeloxifene.\(^7\) This study reported endometrial thickening as a significant adverse effect following 12 months of levormeloxifene use and found the effect to be reversible.\(^7\)

Hysteroscopic examinations showed that levormeloxifene was related to increased incidence of edema, vascularization and cysticity.

These reports have deterred the use of levormeloxifene in postmenopausal women but its use in age group of 20-45 years as an oral contraceptive is still popular for reasons cited above.\(^4,6,7\) In our case, there was proliferation and decidualisation of endometrium presenting as AUB along with polypoidal growth of endometrium possibly following prolonged unsupervised use of levormeloxifene. However, a direct causal relationship could not be established.

In the reported case, the young female had been using levormeloxifene for 10 years in an unsupervised fashion. Levormeloxifene could have possibly decidualized endometrium and instigated polyploidal proliferation of endometrium along with microglandular hyperplasia of cervix. Although this complication may be rare, any unregulated use of the drug requires periodic medical supervision in view of potential consequences. It also remains to be seen, whether the decidual changes are reversible following cessation of drug use in young women. There is also need to develop better immunodiagnostic methods for detection of microglandular hyperplasia of cervix and it’s distinction from malignancies.

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