INTRODUCTION:

AUB is defined as the bleeding from the genital tract which is beyond the normal limits of quantity, duration and frequency. Altered hypothalamic-pituitary-ovarian function or alteration in the prostaglandin levels are the main causes for AUB. AUB is more common in anovulatory cycles than in ovulatory cycles.

Medical management is the first therapeutic option followed by minimally invasive procedures like endometrial ablation, in the management of AUB. Hysterectomy is the last resort, as it results in unnecessary morbidities like premature menopause, bladder and bowel disturbances. Common drugs used for the medical management of AUB includes non-steroidal anti-inflammatory drugs, antifibrinolytics, progesterone, estrogen-progesterone combinations, LNG-IUS, danazol and GnRH analogues. Non steroidal anti-inflammatory drugs and antifibrinolytics reduces menstrual blood loss by 25% to 35% and 50% respectively. Estrogen-progesterone combinations and LNG-IUS reduces menstrual blood loss by 50% and 80% respectively. Progesterone only preparations are ineffective in the management of ovulatory heavy menstrual bleeding and need to be used in high doses. Danazol and GnRH analogues, though highly effective, are intended for short term use, because of its potential side effects. Hence, there is a need for a drug which is highly effective, and can be used safely on a long term basis without side effects.

The ideal drug in perimenopausal women is one that has no uterine stimulation, prevents bone loss, has no risk of breast cancer, has positive effect on lipids and cardiovascular system and maintains cognitive function of brain. Ormeloxifene is a benzopyran, selective estrogen receptor modulator (SERM). It acts as an antagonist on uterus and breast and an agonist on vagina, bone, vascular endothelium and brain tissue. The SERM activity is intrinsic to each ER ligand, which accomplishes its unique profile by specific interactions in the target cell, leading to tissue specific actions. By its effect on the vascular endothelium, it leads to decrease in the menstrual blood loss. It causes an asynchrony in the menstrual cycle between the ovulation and development of endometrium. It inhibits estrogen mediated priming and proliferation of endometrium.

MATERIALS AND METHODS:

It is a prospective study conducted between July, 2014 to June, 2017 in the Institute of Social Obstetrics and Government Kasthurba Gandhi hospital for women and children, Triplicane.100 women over the age of 35 years who have completed their family and presenting with AUB were enrolled in the study, after ruling out any uterine pathology, congenital malformation and other organic causes for AUB. They were treated with tablet ormeloxifene 60mg twice weekly for the initial 3 months and then once a week for another 3 months. Results: 90% of treated women showed marked improvement, 8% opted for hysterectomy and 2% opted for trial with LNG-IUD. There was statistically significant improvement in haemoglobin level. Only 5% developed side effects like headache and nausea.

Key words: Abnormal uterine bleeding, Ormeloxifene, Haemoglobin status, Endometrial thickness
investigations to rule out any uterine pathology, congenital malformation and other organic causes for AUB. Complete blood count, coagulation profile, thyroid profile, blood sugar, liver function test, renal function test, ultrasonogram of the pelvis and transvaginal ultrasound measurement of endometrial thickness was done. Their demographic profiles were collected.

The following were the exclusion criteria – leiomyoma, endometriosis, malignancies of the genital tract, medical disorders like liver diseases, renal diseases, thyroid disorders, coagulopathies, pregnancy, IUCD or pill users, lactating women in the first six months of delivery, history of abortion within last three months and hypersensitivity to drugs.

Pretreatment evaluation
Two pretreatment baseline menstrual cycles were compared with cycles after treatment with ormeloxifene for 6 months.

Parameters assessed were
a. Haemoglobin estimation
b. Endometrial thickness in the proliferative phase by transvaginal ultrasonography. (Women with endometrial thickness between 9.4 to 14.5 mm were included in the study).
c. Menstrual blood loss by pictorial blood loss assessment chart (score of >100 corresponds to more than 80 ml of menstrual blood loss. Women with PBAC score of >150 were included in the study).

Treatment protocol
Written informed consent was obtained from all the women included in the study. They were treated with tablet ormeloxifene 60 mg twice weekly for the initial 3 months and then once a week for another 3 months. The enrolled women were asked to maintain menstrual calendar and were reviewed at monthly interval. They were instructed to use sanitary napkins with similar absorption capacity. At each visit, they were enquired in detail about the menstrual history, subjective improvement and side effects experienced, mean blood loss assessment done using PBAC score, and physical examination done. These women were followed up for a total period of 6 months.

Post treatment outcome assessment:
Primary outcome
a. Haemoglobin estimation
b. Endometrial thickness in the proliferative phase by transvaginal ultrasonography
c. Menstrual blood loss

Secondary outcome
Acceptability of ormeloxifene among the patients treated for AUB.

RESULTS AND ANALYSIS

Age wise distribution of cases under study
10% were between 30 – 35 years, 42% were between 36 - 40 years, 28% were between 41 – 45 years and 28% were between 46 – 50 years.

Number of days of menstrual flow of cases under study
36% had 4 – 6 days flow, 47% had 7 – 9 days flow and 17% had more than 9 days flow.

Cycle length of cases under study
52% had 28 – 30 days cycle, 28% had 31 – 33 days cycle and 20% had 34 – 36 days cycle.

Duration of complaints of cases under study
28% had complaints for less than 6 months, 62% for 6 – 12 months, 10% for 12 – 18 months.

Socioeconomic status of cases under study
1% belong to socioeconomic class 2, 90% belong to class 3, 9% belong to class 4.

Duration of treatment with ormeloxifene (Fig – 1)
98% continued treatment for 6 months, whereas 2% discontinued treatment

Fig 1 : Compliance to treatment with Ormeloxifene

COMPLIANCE TO TREATMENT
Amenorrhoea with ormeloxifene treatment
7% of the treated women had amenorrhoea.

Hypomenorrhoea with ormeloxifene treatment
Another 7% of the treated women had hypomenorrhoea.

Nausea associated with ormeloxifene treatment
Only 5% had nausea while on treatment with ormeloxifene.

Headache associated with ormeloxifene treatment
Only 5% had headache while on treatment with ormeloxifene.

Comparison of pre and post treatment Haemoglobin level (Fig – 2)
When compared to pretreatment Haemoglobin, there was
1.38gm% increase in Haemoglobin at the end of 3 months,
and 0.547gm% at the end of 6 months. Both the values are
statistically significant (p<0.001).

Fig 2: Comparison of pre and post treatment Haemoglobin level

Comparison of PBAC score pretreatment and posttreatment with ormeloxifene (Fig – 3)
The pretreatment PBAC score in the study group was between 190 and 210. The mean pre treatment PBAC score was 206.88. The mean post treatment PBAC score was 94.55 and 77.96 at the end of 3 months and 6 months respectively.

Fig 3: Comparison of PBAC score pretreatment and posttreatment with ormeloxifene

Comparison of pretreatment and post treatment endometrial thickness with ormeloxifene (Fig – 4)
The pretreatment endometrial thickness in the study group was between 9.4mm and 12.5mm. The mean pre treatment endometrial thickness was 11.067mm. The mean post treatment endometrial thickness was 10.103mm after 3 months and 8.956mm after 6 months. Based on the estimated marginal means, the mean difference is significant at the 0.5 level.

Fig 4: Comparison of pretreatment and posttreatment endometrial thickness with ormeloxifene

Overall outcome of treated women (Fig – 5)
In our study, 90% showed marked improvement with ormeloxifene treatment, only 5% showed mild improvement while another 5% did not respond to treatment. 8% of them underwent hysterectomy with the indication being AUB – not responding to medical management. The remaining 2% opted for a trial with LNG-IUS.

Fig 5: Overall outcome of treated women

CONCLUSION:
Ormeloxifene, a designer drug significantly reduced the menstrual blood loss in patients with AUB as
evidenced by decrease in PBAC score along with significant rise in haemoglobin levels, thus improving the quality of life of women with AUB. It resulted in decrease in duration as well as quantity of menstrual blood flow. Amenorrhoea/hypomenorrhoea, with the use of ormeloxifene were desirable side effects in the perimenopausal women and in women unfit or unwilling for surgery. It also provided relief from premenstrual syndrome in perimenopausal women. Further, there was a reduction in the proportion of treated women opting for hysterectomy, thus avoiding morbidities associated with surgery.

Ormeloxifene is a non-steroidal and non hormonal drug which is metabolically and pharmacologically safe and is protective to both endometrium and breast. The ease of administration of the drug improves patient compliance and acceptability. It causes significant reduction in menstrual blood loss and decrease in endometrial thickness. The marked relief of symptoms and negligible side effects results in higher satisfaction. Furthermore, this novel drug is available free of cost in all Government Hospitals in the name of “CHAYYA”. So, Ormeloxifene should be the drug of choice in women who have completed their child-bearing but wishing to retain their menstrual function and in perimenopausal women presenting with AUB.

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REFERENCES: