

Ormeloxifene: Boon to perimenopausal Dysfunctional Uterine Bleeding (DUB) women in avoiding hysterectomies

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Abstract:

Aim and objective: To observe effect of ormeloxifene for treatment of perimenopausal Dysfunctional Uterine Bleeding (DUB) women and follow up in terms of avoiding hysterectomies and to compare ormeloxifene with norethisterone in terms of relief of symptoms, patient acceptability and complications. **Material and Methods:** 300 cases of DUB from two hospitals who have completed child bearing and are between 40-55 years were given Ormeloxifene and Norethisterone during period January 2009 to December 2012 (3 years). Ormeloxifene group (n=150) received 60 mg twice weekly for 12 weeks followed by once weekly for 3 months initially. Norethisterone (n=150) group received 5mg twice a day for 12 days in every cycle for 6 months. **Results:** 123(82%) women in the ormeloxifene administered patients and 45(30%) of norethisterone group had marked relief of symptoms with significant reduction of blood clots, reduction of Pictorial Blood Assessment Chart (PBAC) scores (=25.36, P value=0.0001, extremely significant). Side effects/complications included amenorrhea (=0.614, P value=0.433, not significant), irregular periods (=0.614, P value=0.1102, not significant). 54(36%) of ormeloxifene group and 36(24%) had bout of bleeding after treatment was stopped (=1.190, P value=0.2752, not significant). Dosage schedule of ormeloxifene administration facilitated compliance and acceptability. **Conclusion:** Ormeloxifene has better compliance and acceptability with marked relief in symptoms. Women who underwent hysterectomy after treatment were significantly less in ormeloxifene group. Though the study size is small, it highlights the role of ormeloxifene in reducing menorrhagia and avoiding surgery in perimenopausal women with proper follow up.

Keywords: ormeloxifene , hysterectomy.

INTRODUCTION:

Hysterectomy is a major surgical procedure that has some risks and benefits, and affect a overall health of woman by changing the hormonal balance for the whole life.

Because of this, hysterectomy is normally preferred as a last option to treat certain complicated uterine/reproductive system

disorders. Such conditions include, but are not limited to:

- uterine, cervical, ovarian, endometrium cancers or some benign tumors, like uterine fibroids that do not respond to more conservative treatment options.
- Severe and intractable endometriosis (growth of the uterine lining outside the uterine cavity) and/or adenomyosis
- Chronic pelvic pain, when medicinal or other surgical options have been failed.
- Postpartum to eliminate either a complicated case of placenta praevia or placenta percreta, as well as a last choice in case of excessive obstetrical haemorrhage.
- Several forms of vaginal prolapse.

But in recent scenario, hysterectomy is well performed in non-indicated cases as well as in cases for which other forms of treatment is available. Major reasons for these are:

- Cost effectiveness of hysterectomy
- Less requirement of follow up if done for benign reason
- Women think that quality of life will be better when they will get rid of their menorrhagia
- Cancer phobia
- Other forms of treatment are not discussed with patient

- Other forms of treatment require follow up and are costly

Most common indications for hysterectomies worldwide are menorrhagia, fibroid uterus and prolapse but there is alarming increase for indications like chronic pelvic pain, pelvic inflammatory disease and asymptomatic fibroids.(1) Though there is lesser incidence of hysterectomies in developing countries in comparison to developed countries but it seems the tip of iceberg due to under reporting of cases. There are extrapolated statistics used for calculation of the incidence.

Incidence in various regions:

Approximately 600,000 hysterectomies are performed annually in the United States and an estimated 20 million U.S. women have had a hysterectomy (2). During 2000–2004 the overall hysterectomy rate for United States female civilian residents was 5.4 per 1,000 women (3). During this time period, the overall rate of hysterectomy decreased slightly(4,5). Hysterectomy rates were highest in women aged 40–44 years. According to the National Center for Health Statistics, of the 617,000 hysterectomies performed in 2004, 73% also involved the surgical removal of the ovaries. In the United States, 1/3 of women can be expected to have a hysterectomy by age 60. There are currently an estimated 22 million people in the United States who have undergone this procedure. An average of 622,000 hysterectomies a year has been performed for the past decade. In the UK, 1

in 5 women are likely to have a hysterectomy by the age of 60, and ovaries are removed in about 20% of hysterectomies. The total number of hysterectomies performed in UK NHS hospitals in 2011/2012 is 56,976. Of this, at least 35,396 are abdominal hysterectomies and at least 18,154 are vaginal hysterectomies. In developing countries, a lower rate (4-6%) has been reported.

To avoid irrational hysterectomies, we considered the role of Ormeloxifene which is effective as well as economic in perimenopausal DUB women in avoiding hysterectomies.

Ormeloxifene is a SERM, or selective estrogen receptor modulator. In some parts of the body, its action is estrogenic (e.g., bones), in other parts of the body, its action is anti-estrogenic (e.g., uterus, breasts) It causes an asynchrony in the menstrual cycle between ovulation and the development of the uterine lining.

MATERIAL AND METHODS:

300 cases of DUB (Dysfunctional uterine bleeding) from two hospitals who have completed child bearing and are between 40-55 years were given Ormeloxifene and Norethisterone during period January 2009 to December 2012 (3 years). Ormeloxifene group (n=150) received 60 mg twice weekly

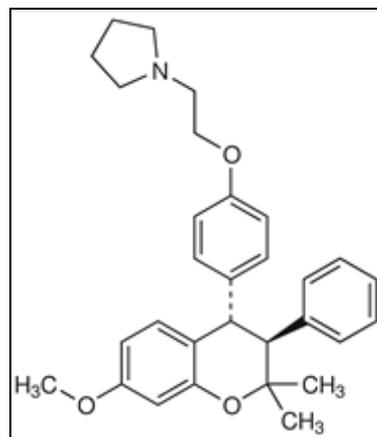


Fig.1

Ormeloxifene molecule

for 12 weeks followed by once weekly for 3 months initially. Norethisterone (n=150) group received 5mg twice a day for 12 days in every cycle for 6 months. Before starting therapy, ultrasound, hysteroscopy and endometrium sampling for histopathology was done and repeated at the end of follow up. Initial evaluation was done and systemic diseases, diabetes, liver disorders, thyroid disorders, coagulation disorders were ruled out. A detailed gynecological examination excluded any uterine pathology. Endometrial thickness and transvaginal sonography was carried out every three months to study the response of the endometrium to the drug. The side effects and complications of the drug ormeloxifene were noted and reliefs of symptoms, patient compliance were compared with norethisterone. All patients were followed till 6 months. The side effects and complications of drug Ormeloxifene were noted and relief of symptoms and patient acceptability were compared with Norethisterone. Women who were benefitted with ormeloxifene continued the

same. Women who required hysterectomy despite of treatment were observed. Chi square test was applied and P value Calculated.

RESULTS:

123(82%) women in the ormeloxifene administered patients and 45(30%) of norethisterone group had marked relief of symptoms with significant reduction of blood clots, reduction of Pictorial Blood Assessment Chart (PBAC) scores (= 80.208, p value < 0.001, highly significant). The pretreatment median PBAC score was 423 (range 169-835) in ormeloxifene group and 410 in norethisterone group. Median PBAC reduced to 85 (range 0-730) and 25(range 0-310) at 3 and 6 months in case of ormeloxifene group whereas in norethisterone group, it reduced to 123 (range 0-730) and 45(range 0-310) at 3 and 6 months, respectively. During the 36-month study period, 20 women from ormeloxifene group underwent hysterectomy and 7 were lost to follow up. In norethisterone group, 40 women underwent hysterectomy, 40 women resorted to other treatment (other than ormeloxifene) and 15 were lost to follow up. Side effects/complications included amenorrhea (=6.284, p value 0.0122(<0.05) significant), irregular periods (= 3.038 p value 0.0813(>0.05), Not significant. 54(36%) of ormeloxifene group and 36(24%) had bout of bleeding after treatment was stopped (=4.587 p value 0.0322(<0.05) significant). 8(5.3%) women in each group suffered from stress urinary incontinence (=0.000, p value 1.000 (>0.05) not significant). Dosage schedule of

ormeloxifene administration facilitated compliance and acceptability.

DISCUSSION:

A medical management is the first line of therapy for dysfunctional uterine bleeding. The agents that have been used to treat menorrhagia include iron, cyclooxygenase inhibitors, desmopressin, antifibrinolytics, gonadotropin-releasing hormone agonists, androgens, combined oral contraceptives, and progestins (6,7) . Progestins can be administered systemically or locally and they may be given cyclically or continuously. The increased use of effective medical therapies has the potential to reduce the number of surgical procedures, such as endometrial ablation and hysterectomy.

Dysfunctional uterine bleeding is the diagnosis in a majority of the cases of menorrhagia. The symptom of menorrhagia accounts for a significant proportion of the referrals to gynecologists. There is no hormonal defect in dysfunctional uterine bleeding; however, disturbances in the endometrial mediators have been noted. A majority of the cases are associated with ovulatory cycles when the cycle control is not an issue, and they can thus be treated with non-hormonal methods such as prostaglandin synthetase inhibitors and antifibrinolytics. Those patients with anovulatory cycles may benefit from an exogenous control of the pattern of bleeding by the use of hormonal preparations. When an effective contraception is also required, the uses of either a combined oral contraceptive or the levonorgestrel releasing

Intrauterine System (IUS) are the suitable choices.

In our study, significant reduction in PBAC Score was seen similar to other studies (8,9). Ormeloxifene has better compliance and acceptability as symptoms are reduced to great extent (10). In comparison to norethisterone, it provided better symptomatic relief. Women who underwent hysterectomy in ormeloxifene group were almost half of that of norethisterone group. Acceptability can be seen as none of the women resorted to other methods and were satisfied with ormeloxifene. Amenorrhea was seen in 19 women in ormeloxifene group and 6 women in other one which was significant. These women acquired menopause as they were in climacteric phase. Irregular bleeding was seen in both the groups but it was not significant. Only significant problem seen with ormeloxifene is heavy bout of bleeding when shifting the dose from 60 mg twice weekly to once weekly at 12 weeks. Heavy bout was seen between 3-6 months also in ormeloxifene group. Stress urinary incontinence was seen in equal number of women in both the groups and was insignificant. Study by kriplani et al showed similar results(8).

CONCLUSION:

Ormeloxifene has better compliance and acceptability with marked relief in symptoms. Irregular bleeding and amenorrhoea was seen more with norethisterone group. Though bout of bleeding was observed in some patients with ormeloxifene, it was not significant. Women

who underwent hysterectomy after treatment were significantly less in ormeloxifene group. Though the study size is small, it highlights the role of ormeloxifene in reducing menorrhagia and avoiding surgery in perimenopausal women with proper follow up.

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Ethical approval: The study was approved by the institutional ethics committee

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Table 1. Showing symptomatic relief (Reduction of PBAC scores) in two groups

| | Ormeloxifene Group (n=150) | Norethisterone group (n=150) |
|--|---------------------------------------|---|
| Symptomatic relief present (reduction of PBAC scores) | 123(82%) | 45(30%) |
| Symptomatic relief not present | 27(18%) | 105(70%) |

*Chi square value 80.208, p value <0.001 (highly significant)

Table 2. Showing number of women who underwent hysterectomy in two groups

| | Ormeloxifene Group (n=150) | Norethisterone group (n=150) |
|---|---------------------------------------|---|
| Finally Underwent hysterectomy | 20(13.3%) | 40(26.7%) |
| Resorted to other treatment and were satisfied | none | 40 (26.7%) |
| Lost to follow up | 7 (4.7%) | 15 (10%) |

Table 3. Showing women with amenorrhea in two groups

| | Ormeloxifene Group (n=150) | Norethisterone group (n=150) |
|---------------------------|-----------------------------------|-------------------------------------|
| Amenorrhea present | 19(12.7%) | 6(4%) |
| Amenorrhea absent | 131(87.3%) | 144(96%) |

Chi square value 6.284, p value 0.0122(<0.05) significant

Table 4. Showing women with irregular bleeding in two groups

| | Ormeloxifene Group (n=150) | Norethisterone group (n=150) |
|-----------------------------------|-----------------------------------|-------------------------------------|
| Irregular bleeding present | 23(15.3%) | 36(24%) |
| Irregular bleeding absent | 127(84.6%) | 114(76%) |

* Chi square value 3.038 p value 0.0813(>0.05) Not significant

Table 5. showing women with heavy bout of bleeding in two groups

| | Ormeloxifene Group (n=150) | Norethisterone group (n=150) |
|---------------------------------------|-----------------------------------|-------------------------------------|
| Heavy bout of bleeding present | 54 (36%) | 36 (24%) |
| Heavy bout of bleeding absent | 96(64%) | 114(76%) |

* Chi square value 4.587 p value 0.0322(<0.05) significant

Table 6. showing stress urinary incontinence in two groups

| | Ormeloxifene Group (n=150) | Norethisterone group (n=150) |
|--|-----------------------------------|-------------------------------------|
| Stress urinary incontinence present | 8(5.3%) | 8(5.3%) |
| Stress urinary incontinence Absent | 142(94.6%) | 142(94.6%) |

*Chi square value 0.000 p value 1.000 (>0.05) not significant

Table 7. showing women in two groups with statistical analysis

| | Ormeloxifene Group (n=150) | Norethisterone group(n=150) | Chi square value | P value | Remarks |
|--|----------------------------|-----------------------------|------------------|---------------|--------------------|
| Symptomatic relief(reduction of PBAC scores) | 123(82%) | 45(30%) | 80.208 | <0.001 | Highly significant |
| Amenorrhea | 19(12.7%) | 6(4%) | 6.284 | 0.0122(<0.05) | Significant |
| Irregular bleeding | 23(15.3%) | 36(24%) | 3.038 | 0.0813(>0.05) | Not significant |
| Heavy bout of bleeding | 54 (36%) | 36 (24%) | 4.587 | 0.0322(<0.05) | Significant |
| Stress urinary incontinence | 8(5.3%) | 8(5.3%) | 0.000 | 1.000(>0.05) | Not significant |

Figure no.1

PBAC Scoring System

| Pads | | |
|----------------|---|---|
| 1 point | For each lightly stained pad |  |
| 5 points | For each moderately stained pad |  |
| 20 points | For each completely saturated pad |  |
| Tampons | | |
| 1 point | For each lightly stained tampon |  |
| 5 points | For each moderately stained tampon |  |
| 10 points | For each completely saturated tampon |  |
| Clots/Flooding | | |
| 1 point | For each small clot (Australian 5 cent coin) | |
| 5 points | For each large clot (Australian 50 cent coin) | |
| 5 points | For each episode of flooding | |

Figure no.2 showing women in Ormeloxifene Group with statistical analysis

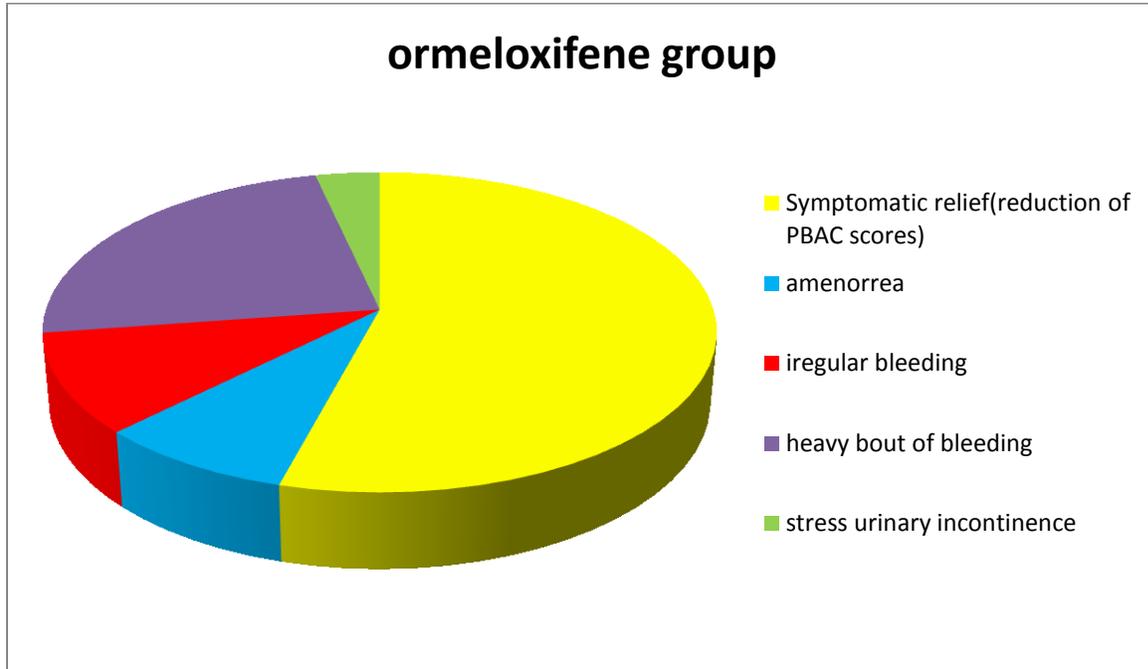


Figure no.3 showing women in Norethisterone group with statistical analysis

