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Original Research Article

Study of acceptability, efficacy and side effects of non-steroidal contraceptive ormeloxifene and its comparative evaluation with combined oral contraceptives

Neena Gupta[1], Eram Siddiqui[2]*, Divya Dwivedi[1], Uruj Jahan[1]

[1]Department of Obstetrics and Gynecology, GSVM Medical College, Kanpur, Uttar Pradesh, India
[2]Department of Obstetrics and Gynecology, Sanjay Gandhi Postgraduate Institute, Lucknow, Uttar Pradesh, India

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***Correspondence:**
Dr. Eram Siddiqui,
E-mail: eram.luck@gmail.com

ABSTRACT

Background: Despite their efficacy, COCs are associated with various side effects, including mood changes, weight gain, and cardiovascular risks, which can limit their acceptability among some women. These challenges have prompted ongoing research into alternative contraceptive methods that offer effective pregnancy prevention while mitigating hormonal side effects. In this context we conducted a study to assess the acceptability, effectiveness, and side effects of the non-steroidal contraceptive ormeloxifene for contraception, and to compare it with combined oral contraceptives (COCs).
Methods: The study was a prospective longitudinal study carried out in the department of obstetrics and gynecology (UISEMH), GSVM medical college, Kanpur, Uttar Pradesh, India.
Results: The study included two groups: 90 women opted for ormeloxifene (postpartum, post-abortal, and interval cases) as their contraceptive method, while another 53 women chose combined oral contraceptives (post-abortal and interval cases). The majority of participants in both groups were aged between 26 and 30 years. Patients were monitored for one year, with assessments conducted at the 3rd, 6th, and 12th months following initiation of the oral pills, and no participants were lost to follow-up. The study found statistically significant differences, particularly noting an 85.5% continuation rate with ormeloxifene, which was markedly higher compared to 39.6% observed with COCs.
Conclusions: Ormeloxifene is a safe non-steroidal contraceptive option for pregnancy spacing and demonstrates comparable acceptability to COCs. Side effects beyond menstrual issues (such as weight gain, nausea, vomiting, and headache) are the primary reasons for discontinuation of COCs. Both hormonal (combined oral contraceptives) and non-hormonal (ormeloxifene) oral contraceptive pills are safe and effective methods of contraception.

Keywords: Combined oral contraceptives, Ormeloxifene

INTRODUCTION

Contraception has played a pivotal role in shaping women's health and reproductive choices throughout history. From ancient herbal remedies to modern pharmaceutical innovations, the landscape of contraceptive options has continuously evolved to meet the diverse needs and preferences of women worldwide.

The 20th century witnessed a revolutionary breakthrough with the development of hormonal contraceptives. India pioneered the world's first National Programme for Family Planning in 1952, marked a transformative moment, offering women a reliable method based on hormonal regulation to prevent pregnancy. Combined oral contraceptive pills (COCs) include low doses of two synthetic hormones- progesterone and estrogen- that

mimic natural hormones in the female body, in order to inhibit ovulation and alter cervical mucus, establishing a highly effective contraceptive option that revolutionized family planning practices globally.[1]

It is well known now that Family Planning is important not only for achieving population stabilization but is also central to improve the maternal and new born health and survival.[2]

Nonsteroidal oral contraceptives (ormeloxifene)

Non-steroidal contraceptives represent a significant advancement in contraceptive technology, offering alternatives to hormonal methods. Ormeloxifene, a selective estrogen receptor modulator (SERM), exemplifies this innovation by utilizing a non-hormonal mechanism to prevent pregnancy.[3] Approved for contraceptive use in several countries, Ormeloxifene works by thickening cervical mucus and altering the endometrium, inhibiting sperm entry and fertilized egg implantation without directly affecting ovarian function.

METHODS

The present study is prospective longitudinal study conducted in the outpatient department (OPD) of the department of obstetrics and gynecology at Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India from January 2020 to September 2021.

Inclusion criteria

All reproductive age group (18-45 years of age) willing to use COC or ormeloxifene as a contraceptive in postpartum, postabortal or interval period and willing to participate and follow up in the study.

Exclusion criteria

Category 3/4 patients (according to MEC criteria), liver impairment or jaundice, known case of any kidney disease, PCOS, tuberculosis, cervical hyperplasia, severe allergic states were excluded.

Methodology

A total of 360 healthy women meeting the inclusion criteria and regularly attending the outpatient departments of UISEMH, department of obstetrics and gynecology, GSVM Medical College, Kanpur, were counselled regarding contraceptive methods. Out of these, 200 women consented to oral contraception, while 160 opted for alternative methods. Among the 200 women who consented to oral contraception, 143 met the inclusion criteria, with 53 choosing combined oral contraceptives (COCs) and 90 opting for non-steroidal contraception (ormeloxifene). Informed consent was obtained, and comprehensive counselling included discussions on indications, benefits, and potential side effects. Detailed clinical histories, especially focusing on menstrual cycles, were recorded, and these patients did not use other forms of contraception.

Pre-initiation assessment of women

All participants underwent initial comprehensive physical and gynecological examinations, and baseline investigations were conducted to detect any abnormalities. Following the initiation of the first pill, which was well tolerated with no adverse effects reported, all women were instructed to return for follow-up after three months or earlier if they experienced any specific issues related to the pill or gynecological concerns.

Initiation

OCPs

Mala-N: first dose at day 1 of menstrual cycle: 1 tablet daily for 21 days followed by 7 days of ferrous fumarate.

Ormeloxifene

First dose at day 1 of menses. It is to be taken 2 fixed days a week for 3 months followed by 1 fixed day/week every month thereafter.

Statistical analysis was performed by using percentage, mean, standard deviation, chi-square test.

RESULTS

The highest number of users in both groups falls within the age range of 26-30 years (Table 1), with an average parity of 2 (Table 1). Ormeloxifene showed good acceptance during the postpartum period (Table 1), while acceptance rates during the post-abortal and interval periods were comparable between the two groups of oral contraceptives (Tables 2 and 3).

Table 1: Socio-demographic variables of the participants.

Age	Group 1 (ormeloxifene) n=90 (%)	Group 2 (COC's) n=53 (%)
≤20 years	2 (2.22)	2 (3.77)
20-25 years	38 (42.22)	22 (41.50)
26-30years	46 (51.11)	25 (47.16)
≥31 years	4 (4.44)	4 (7.54)
Nulliparous	2 (2.21)	1 (1.88)
1	28 (31.11)	15 (28.30)
2	43 (47.77)	28 (52.83)
≥3	17 (18.88)	9 (16.98)
Postpartum	35 (38.88)	-
Post abortal	17 (18.88)	16 (30.18)
Interval	38 (42.22)	37 (69.81)

Table 2: Comparative evaluation between acceptability of ormeloxifene and COC's in interval period.

Groups	Subjects counselled	Subjects received	Acceptability (%)	P value
Group1 (ormeloxifene)	90	38	42.2	0.8813
Group 2 (COC's)	90	37	41.1	

Table 3: Comparative evaluation between acceptability of ormeloxifene and COC's in post abortal period.

Groups	Subjects counselled	Subjects received	Acceptability (%)	P value
Group1 (ormeloxifene)	40	17	42.5	0.8214
Group 2 (COC's)	40	16	40	

Table 4: Comparative evaluation of continuation between the two groups.

Groups	After 3 months (%)	After 6 months (%)	After 1 year (%)
Group1 (ormeloxifene)	100	96.6	85.5
Group 2 (COC's)	94.3	75.4	39.6
95% confidence in level	0.1580 to 15.4236	9.8487 to 34.4321	29.8801 to 59.2632
chi square	5.204	14.90	32.33
P value	<0.05	<0.001	<0.0001
Inference	Significant	Significant	Significant

Table 5: Comparative analysis of menstrual patterns of non-steroidal contraceptives (ormeloxifene) in postpartum, postabortal and interval period.

	Postpartum n=35 (%)	Interval n=38 (%)	Post-abortal n=17 (%)
Delayed cycles	8 (22.8)	7 (18.4)	3 (17.6)
Oligomenorrhoea	3 (8.5)	3 (7.8)	1 (5.8)
Amenorrhoea	2 (5.7)	2 (5.2)	1(5.8)
Menorrhagia	0	1 (2.6)	0
Irregular menstrual cycles	4 (11.4)	3 (7.8)	2 (11.7)

Table 6: Comparative analysis of side effects between both the groups.

	Group 1 ormeloxifene (n=90) (%)	Group 2 (COC's) (n=53) (%)	P value
Menstrual irregularities	10 (11.1)	4 (7.5)	0.001754
Breakthrough bleeding	0	6 (11.3)	
Nausea/vomiting	1 (1.1)	5 (9.4)	
Headache	1 (1.1)	4 (7.5)	
Weight gain	0	7 (13.2)	
Total	12	26	

There were more dropouts observed among subjects using COCs (Figure 1), and this trend increased with the duration of usage. Major reason for drop out among users of ormeloxifene is menstrual changes, while among users of COC's other side effects (weight gain, nausea, vomiting, headache) are the reason for discontinuation (Figure 2), thus, continuation rates are higher among users of Ormeloxifene (Table 4). Maximum users of non-steroidal contraceptive (ormeloxifene) report delayed cycles as the most common side effect. Menstrual cycles tend to settle down to a rhythm once the body gets used to the drug (Table 5). The frequency of menstrual complaints decreases with time and at the end of the study only 11% users had menstrual complaints (Figure 3).

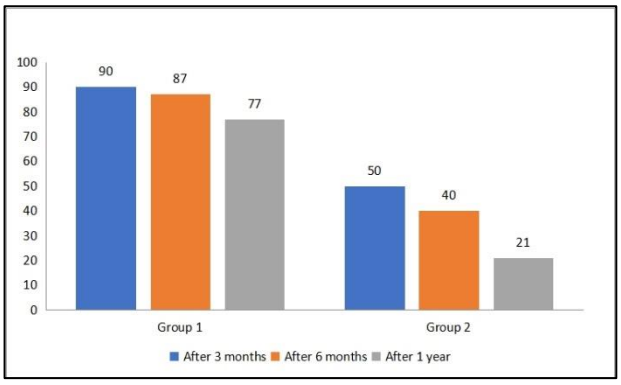

Figure 1: Dropout rates of both the groups.

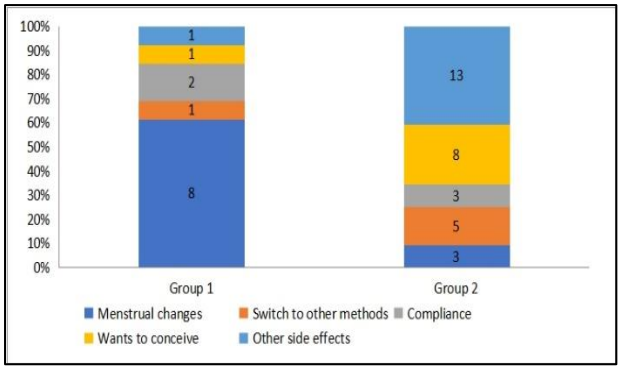

Figure 2: Comparative evaluation for reasons for dropout rate in both the groups.

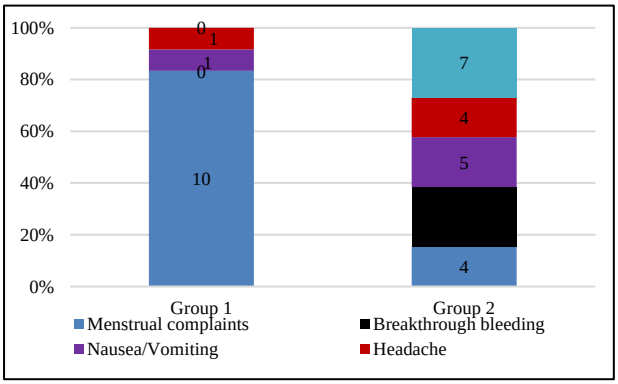

Figure 3: Comparative evaluation for side effects in both the groups.

DISCUSSION

In our study, the majority of subjects (51.1%) who chose ormeloxifene as their contraceptive method belonged to the age group of 26-30 years, with 42.2% falling into the 20-25 years age bracket, highlighting a significant proportion of reproductive-age individuals with an unmet need for contraception. Together, these age groups (20-30 years) constituted 93.3% of contraceptive users in our study. This finding aligns with previous research: reported 85% of users in the 20-30 years age group, while another study found 67% in the 26-35 years age group, and study by Qureshi et al noted a majority (18.9%) in the 25-29 years age group, similar to our study.[4-6] However, a study reported that 60.1% of acceptors belonged to the 20-24 years age group.[7]

Regarding parity, in our study, a majority of contraceptive users were in parity P2 (47.7%) followed by P1 (31.1%), while very few (18.8%) subjects in P3 opted for oral contraception, as this group typically required more permanent contraception methods. This trend correlates with findings with study, where the maximum unmet need for contraception was observed in parity P1.[8] Regional variations may influence family planning decisions, as evidenced by research from study which showed a majority (74.65%) of multiparous women in their study, contrasting with study, where 93% of subjects were primiparous, and study where P1-P3 constituted 68.75% of subjects.[4,7,9]

In terms of socioeconomic status, our study found that 40% of ormeloxifene users belonged to class 3 according to the BG Prasad scale, indicating moderate socioeconomic status. This differs from study by Ganguli et al, where maximum users were in classes 4 and 5, suggesting a higher socioeconomic profile.[4]

Furthermore, our study analysed the distribution of all demographic parameters between the two groups using chi-square tests and found no statistically significant difference (p value >0.05). This suggests that demographic characteristics were similarly distributed among the subjects opting for ormeloxifene and those choosing combined oral contraceptives (COCs) in our study.

Acceptability

Out of 200 patients counselled about ormeloxifene, 90 subjects opted for it as their method of contraception, representing a 45% acceptance rate. In contrast, to the study by Qureshi et al which reported a general population acceptability of ormeloxifene at 3.86%.[6]

Among the 130 subjects counselled for combined oral contraceptives (COCs), 53 subjects chose COCs as their method of contraception.

Among users of ormeloxifene, the highest acceptability was observed during the postpartum period (50%) and post-abortal period (42.5%). These findings are consistent with the study, where maximum acceptance was seen among post-abortal (38.35%) and postpartum (36.3%) users.[9] Women in the postpartum and post-abortal groups represent ideal candidates for ormeloxifene due to its non-hormonal nature, less frequent dosing requirements, and safety for breastfeeding mothers. In contrast, combined oral contraceptives cannot be administered immediately postpartum or to lactating females.

A comparative evaluation of continuation rates between the two groups showed higher continuation rates among subjects using ormeloxifene as a method of contraception. A similar study among post-abortal subjects yielded results consistent with our study.[10]

Continuation rates

In our study, the continuity rate after the third dose was 86%, which surpasses the 68.5% reported by Doke et al, but aligns closely with the 85% continuation rate found by another study.[7,9]

Continuation rates among users of combined oral contraceptives (COCs) in our study were 94.3%, 75.4%, and 39.6% at 3 months, 6 months, and 1 year respectively. This contrasts with study by Khan et al, where continuation rates were 57% at 6 months, and study by

Kamalifard et al, which reported rates of 88.96%, 58.01%, and 44.59% at 1, 6, and 12 months respectively.[11,12] Similar to our findings, another study reported continuation rates of 61% at 3 months and 43% at 6 months.[13]

A comparative study between ormeloxifene and COCs conducted by Miuli et al demonstrated higher continuation rates of 91.6% for ormeloxifene users.[10] The primary reason for discontinuation in our study was primarily delayed menstrual cycles, with additional factors including challenges in accessing follow-up care from rural areas, desire for conception, or adoption of alternative methods.

Efficacy

The current study did not detect any instances of failure. Nevertheless, its findings were constrained by a small sample size and a brief follow-up period.

In contrast, study by Ganguli et al documented a success rate of 96.87% (pearl index 3.12).[4] Ormeloxifene demonstrated a failure rate of 1.63% (pearl index 1.83 per 100 woman-years). In comparative evaluation, no failure rates were observed among subjects using combined oral contraceptives.

Side effects

Menstrual changes

The most prevalent side effect reported by users of ormeloxifene is menstrual complaints, which also constitute a significant reason for discontinuation among users. According to Indian national guidelines on oral contraceptive use, approximately 8% of ormeloxifene users experience menstrual delay, typically within the first 3 months of use.

In our study, the highest reported side effect among ormeloxifene users was delayed menstrual cycles, reported by 15% of participants experiencing menstrual complaints. Similar findings were noted in study by Goter et al with 15% side effects, another study by Miuli et al with 13.6% side effects, and while study by Ganguli et al with 12.5% side effects.[4,9,10] In contrast, a study reported a higher incidence of side effects at 25%.[7]

Upon comparative evaluation in our study, it was observed that while menstrual complaints were common, they did not typically lead to discontinuation. The frequency of menstrual complaints decreased over time, and by the end of the first year of use, only 11% of users reported menstrual complaints. These results are consistent with findings from study, where 12% of subjects had menstrual complaints at the end of the study.[7]

In contrast, users of combined oral contraceptives (COCs) in our study commonly reported breakthrough bleeding (11.3%) and irregular menstrual cycles (7.5%) as major menstrual complaints.

Other side effects

Nausea/vomiting

It was observed that nausea vomiting occurred only in 1.1% of women using ormeloxifene. However, in COC users this side effect was the 3rd most common which occurred at 9.4%. A comparative study showed nausea/ vomiting occurred only in 1.66% of women using ormeloxifene while in COC users this side effect occurred at 3, 6 and 12 months at the rates of 8.84%, 14.81% and 3.73%.[10] while study by Khan et al and Kamalifard et al observed 23.4% and 16% of women using COC with side effects of nausea.[11,12]

Headache

Headache was reported as a side effect 1.1% of users of ormeloxifene whereas 7.5 % subjects using COC's reported it as a side effect. The results were consistent with the other studies.[7,10] However study by Khan et al showed a much higher incidence of side effects of 57.4% among COC's users.[11]

Weight gain

In our study weight gain as a side effect was seen only among subjects using COC's and it was the most common side effect seen i.e.13.2 %. In the study by Miuli et al, in women taking COC mean weight in this study was 55.03±2.1 to 60.13±2.1 at pre-initiation and at the end of the study respectively which was found to be statistically of significant difference.[10]

Thus, in our study side effects other than menstrual complaints were noted in 2.2% of the subjects using ormeloxifene. In the study by Doke et al and another study by Nair et al showed other side effects of 1.43%,2.61% respectively.[7,9] While a study which showed higher side effect incidence (i.e.12%).[14]

Among subjects using combined oral contraceptives side effects other than menstrual complaints were reported in maximum number of subjects (30%) and it was the major reason for drop out among them. In our study on comparative evaluation between the two groups of study it was found that these side effects are the major reason for discontinuation among users of combined oral contraceptives. A similar study which showed other side effects among ormeloxifene users to be 1.66% while side effects in combined oral contraceptive users was 9.16%.[10]

Table 7: Present study results and comparison with previous results.

	Year of study	No. of users	Continuation rates (at 3 months, at 6 months, at 1 year)	Menstrual complaints	Other side effects	Failure rates	
Ganguli et al[4]	1995	96	-	12.5%		3.12%	*Study was conducted in post abortal group
Nair et al[7]	2016	153	100%, 97%, 85%	25%	2.61%	2%	
Agrawal et al[14]	2016	25	-	-	12%	-	
Doke et al[9]	2019	146	100%, 89%, 67%	15.06%	1.43%	2.05%	
Miuli et al[10]	2020	120	100%, 98.3%, 91.6%	13.6%	1.66%	0.83%	*study was conducted in post abortal group
Present study	2021	90	100%, 96.6%, 86.6%	15%	2.2%	0	

*The studies by Ganguli et al (1995) and Miuli et al (2020) were conducted on post-abortal women, which may impact the continuation rates and failure rates observed in these populations.

Limitation

Limitation of the study is that although the drug is in use for well over 2 decades in India, it is still advisable to conduct large scale clinical trials over various geographical regions to permanently establish the role of ormeloxifene as an alternative to hormonal OCPs.

CONCLUSION

The introduction of ormeloxifene into India's family planning program under the name "Chhaya" represents a significant government initiative to enhance contraceptive coverage by providing free oral contraception at government centres. Ormeloxifene offers distinct advantages over combined oral contraceptives (COCs) as it can be safely administered to postpartum and breastfeeding women, a crucial demographic in need of contraception in our country. As a safe and effective contraceptive method, ormeloxifene avoids the common side effects associated with COCs. The primary side effect observed is menstrual changes, which tend to diminish over time. Ormeloxifene offers the advantage of not requiring daily intake, although the once-weekly dosing regimen may be prone to occasional lapses. This challenge can be mitigated through comprehensive counselling and regular follow-up. The use of dummy or blank pills between active doses may also help in maintaining a daily pill cycle. Our study reported no instances of pregnancy among users of ormeloxifene, confirming its effectiveness as a contraceptive method. Ormeloxifene stands as a comparable option to combined hormonal pill for contraception with a safe, effective and acceptable characteristics with a better side effect profile in long term users.

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