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Original Article

Obstetrics and Gynaecology Section

A Randomised Controlled Trial Comparing the Efficacy and Side-Effects of Intravaginal Ring (Nuvaring®) With Combined Oral Hormonal Preparation in Dysfunctional Uterine Bleeding

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ABSTRACT

Introduction: Combined Oral Contraceptive (COC) pills are being used in patients of abnormal uterine bleeding, especially adolescents and reproductive age women considering their need for contraception. It decreases the blood loss due to haemostatic effect of estrogen and also regularizes the cycle. Intravaginal route has been found to be effective and acceptable; Gastrointestinal absorption and hepatic first-pass metabolism is avoided and steady, uniform blood concentration is achieved. Bioavailability of estrogen and progestogen through oral and vaginal route are same. The convenience of once-a-month administration is another major advantage.

Materials and Mathods: Sixty women fulfilling inclusion criteria were randomised into 2 groups in 1:1 ratio. In one group (n=30), monthly insertion of Nuvaring®) was done for three consecutive months. Nuvaring® releases 15µg ethinyl estradiol and 120 µg etonogesterol daily. The other group (n=30) received COC pill containing 30µg EE and 150 µg levonorgestrel for three consecutive months. Primary outcome measures were change in menstrual cycle pattern and pictorial Blood Loss Assessment chart (PBAC) score. Other Parameters included side effects, change in haemoglobin and weight. Data was analyzed by statistical software SPSS 20.

Results: Both Nuvaring® and COC were found to significantly decrease blood loss in each cycle. Decrease in PBAC score was more in Nuvaring® group compared to COC, however difference was not significant.

Ideal bleed (IB) was frequently higher for Nuvaring® group than COC in all 3 cycles, although no statistically significant difference was observed between groups (p-value=0.286). Late withdrawl, intermenstural spotting was higher in COC group. Compliance was better and women were more satisfied in Nuvaring® group compared to COC group. Minor side effects like headache, mastalgia, nausea and mood changes were seen in both groups, which were not significant. Continuation rate was significantly higher in Nuvaring® group. 30% women discontinued treatment in OCP group after 3 month compare to 10% in Nuvaring® group.

Conclusion: Present study shows Nuvaring® to be as effective as COC in controlling heavy menstural bleed, better cycle control, with minor acceptable systemic side effects.

Keywords: Abnormal uterine bleeding, Cycle control, Nuvaring, Oral contraceptive pills

INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing. Though the exact incidence is unknown, it is common gynecological problem. Medical management is the first line of treatment in AUB due to non structural and in some cases of structural causes. Non-hormonal and hormonal preparations are available. Hormonal treatment including combined oral pills is well established in AUB. It decreases the blood loss due to haemostatic effect of estrogen and also regularizes the cycle [1]. Treatment of AUB has evolved rapidly over last few years. More recently new hormones in lower doses and other routes of administration are being studied to reduce hormone related side effects and improve patient compliance [2,3]. The various factors affecting the treatment are patient age, etiology, amount of bleeding, contraceptive need and medical problems contraindicating any particular drug. Earlier only the oral route was available but now with the advent of new technology, other options like parenteral, subdermal, nasal, and intravaginal route are also available. Intravaginal route has been found to be effective and acceptable. Gastrointestinal absorption and hepatic first-pass metabolism is avoided and hormones are continuously absorbed by the vaginal mucosa producing steady, uniform blood concentration [1]. Nuvaring® is combined contraceptive hormonal ring, manufactured by Merck, for once-a-month intravaginal application. It releases 15µg Ethinyl Estradiol (EE) and 120 µg etonogesterol per day. While Nuvaring employs the vaginal route of administration, its effects are systemic rather than local. As a result of this, its mechanism of action is comparable to that of a Combined Oral Contraceptive (COC) pill, as are the contraindications. Since the dose of estrogen is halved, systemic exposure to EE with Nuvaring is approximately 50% of that of COC [1,4,5]. The effect on metabolic parameters like lipid profile, glucose etc. is found to be similar to COC [6,7].

Besides contraceptive effect, cycle control is another key factor that affects acceptability and compliance. Various studies have been done in past to demonstrate contraceptive efficacy of Nuvaring and found it comparable to oral pills [1,4-7]; However, till date literature has no study which evaluates efficacy of Nuvaring as compared to Oral contraceptive pills (OCP) in women suffering from AUB.

AIM

Hence this study was planned to compare the efficacy of Nuvaring versus OCP in improving menstrual symptoms in AUB, along with their side effects and patient acceptability.

MATERIALS AND METHODS

A randomized controlled pilot study was conducted in Department of Obstetrics and Gynecology, Guru Teg Bahadur Hospital, New Delhi from July 2012 till June 2013. Prior ethical approval was obtained from the institutional ethical committee. The ctri reference number is REF/2013/01/004495. The funding for the study was through hospital budget. Patients meeting the inclusion criteria were given adequate information about purpose and nature of the study and a written informed consent was obtained from each patient. Detailed history and examination was recorded in the case record performa. Blood investigations and endometrial sampling were done.

Women included were in reproductive age group of 15-45 years, without medical disorders like jaundice, migraine, epilepsy, hypertension or diabetes mellitus, history of thromboembolism, breast or genital tract malignancy, genital prolapse or infections. A total of 60 patients suffering from AUB were recruited for this study and received therapy from single investigator. AUB was defined as any abnormal bleeding from uterus for which no organic pathology of genital tract such as fibroid or adenomyosis is identifiable. They were randomised into two groups (1:1 ratio) based on computer generated random number table by the statistician. First group comprising of 30 women received Nuvaring therapy for three months and the second group (n= 30) received OCPs. In test group, Nuvaring was inserted in the vagina (Initially by the doctor and then patients were taught to insert and remove the ring herself) on the fifth day of the cycle, for next three weeks. At the end of three weeks, it was removed for one week during which withdrawal bleeding occurs. A new ring was inserted after one week of ring free period.

In control group, combined oral tablet containing 30µg EE and 150 µg levonorgesterol (Available as Mala N in government supply, manufactured by Hindustan Latex Ltd.) was started from day 5 of the cycle, one tab daily for 21 days. The black iron tablet which was free of hormone was continued immediately after white tablet for next seven days during which withdrawal bleeding occured. The next packet of Mala N was started immediately after finishing the first packet. In patients, having irregular bleeding, Mala N was started on any day of the cycle, after endometrial sampling was done. Patients was followed up regularly; initially, after one week of starting the therapy and then monthly for three months. Patients were asked to maintain a diary of menstrual pattern, flow, side-effects or any other problem. Menstrual blood loss was recorded as per Pictorial Blood Loss Assessment Chart (PBAC). Withdrawal bleeding was classified as any bleeding/spotting that occurred during ring/pill free period. Ideal bleed (IB) is defined as cycle with a regular withdrawal bleeding in ring or active pill free days of cycle, no early bleed, continuous or irregular bleeding. Any bleeding starting before ring/pill free was termed early withdrawal. Late withdrawal was termed when bleeding continued into the next ring/pill use period. Dysmenorrhea was scored as mild, moderate or severe on the basis of subject's perception. Patient weight and haemoglobin were measured pre study and post study in all.

STATISTICAL ANALYSIS

Primary outcome measures were change in menstrual cycle pattern and PBAC score. Secondary outcomes included side effects, change in haemoglobin and weight. Data was analyzed by statistical software SPSS 20. Baseline demography and clinical profile were analyzed using unpaired student t-test and Chi-square/ Fisher-exact test. Two factor repeated measures ANOVA, taking time as a repeated factor and groups fixed factor. Sphericity assumption was tested using Mauchty test of sphericity and if assumption was violating Green house Geissen adjustment was applied. Interaction between group and time was also tested. The compliance and side effect profile were compared using Fisher-exact test. Change in Haemoglobin and weight were compared using paired t-test separately for each group. Generalized estimating equation technique with logistic link function using unstructured working correction was applied to find trend of Ideal bleed and late bleed pattern.

RESULTS

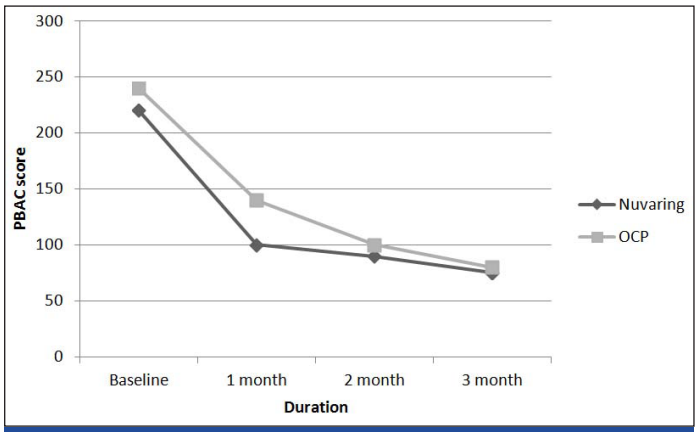
During study, 30 women in Nuvaring group and 28 women in OCP group received treatment. Two patients in OCP group opted out of the study in the first cycle itself, due to personal reasons. Baseline demographic and clinical characteristics of subjects are shown in [Table/Fig-1]. All the subjects were multiparae; there were no significant differences in demographic profile between the two treatment groups.

Parameter	Nuvaring (n=30)	OCP (n=28)	p- value
Age (Mean± SD)	36.00 ±1.14	34.48± 0.92	0 .30
Religion Hindu	18	16	0.878
Muslim	12	12	
Parity Nulliparous	0	0	0.88
Multiparous	30	28	
Duration of symptoms (Years)	1.20±.70	1.18± .62	0 .88
Contraceptive need Yes	19	21	0.228
No	11	07	
Haemoglobin(gm/dl)	10.77± .26	10.15±1.66	0.11
Weight (kg)	56.37±2.20	57.55±1.6	0.66

[Table/Fig-1]: Demographic and clinical characteristics of study population.

Group	Baseline Mean ± SD	Cycle 1 Mean ± SD	Cycle 2 Mean ± SD	Cycle 3 Mean ± SD	p- value Within group*
Nuvaring	214.87± 86.29	102.13± 71.33	87.90± 65.62	87± 42.70	0.000<0.001 F=106.788
OCP	237.57± 86.29	137.68± 61.56	99.00± 66.01	74.75± 51.58	

[Table/Fig-2]: Intergroup and intragroup comparison of PBAC Score.
p-value, between the groups: p= 0.194 (NS)
Interaction between group and time p= 0.301.
*Since sphericity assumption is violating P=0.001, Greenhouse – Geissen adjust was applied.



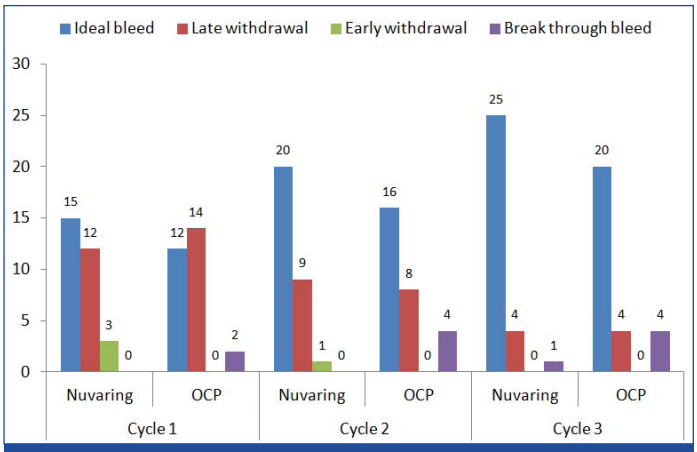
[Table/Fig-3]: Trend of Mean Blood Loss in Nuvaring and OCP.

Irregular heavy menstrual bleeding was the most common presentation; PBAC scoring was calculated to quantify menstrual loss and baseline value was compared to subsequent cycles. Also, bleed pattern in each cycle was noted to see the effect of treatment on cycle regularization. Mean PBAC score at the start of study was 214.87 in Nuvaring and 237.57 in OCP group, which was comparable, with no statistically significant difference [Table/Fig-2]. After completion of first cycle, there occurred 50% reduction in PBAC score in Nuvaring group and 44% in OCP group as compared to baseline score. Although significant reduction in PBAC score was observed in subsequent cycles within both the groups but no significant difference in score was found when Nuvaring group was compared with OCP (p-value = 0.194) [Table/Fig-2,3].

Beside heavy menstrual flow, irregular cycle was common complaint. Use of hormonal therapy not only improved PBAC score but regularized menstrual cycle. [Table/Fig-4] shows the effect of Nuvaring and OCP on patterns of menstrual flow. There was an

Cycle	Ideal bleed n (%)	Late withdrawal n (%)	Early withdrawal n (%)	Break through Bleed n (%)
Cycle 1 Nuvaring	15 (50%)	12 (40%)	03 (10%)	0
OCP	12 (42.8%)	14(50%)	0	02(7%)
Cycle 2 Nuvaring	20 (66.6%)	09(30%)	01(3.3%)	0
OCP	16 (57%)	08(28.5%)	0	04(14%)
Cycle 3 Nuvaring	25 (83.3%)	04(13.3%)	0	01(3.3%)
OCP	20 (71.4%)	04(14.2%)	0	04(14.2%)

[Table/Fig-4]: Menstrual pattern over study period in the groups.



[Table/Fig-5]: Patterns of menstrual flow. Cycle-wise menstrual pattern

Parameters	Nuvaring (N=30)	OCP (N=28)	p-value
Satisfaction	29 (96.7%)	23 (82%)	0.854
Recommendation	27 (90%)	20 (71%)	0.704
Continuation	27 (90%)	20 (71%)	0.488
Discontinuation	03(10%)	08 (28.5%)	0.783
Headache	2(6.7%)	4 (14%)	0.399
Nausea	0	6 (21.4%)	-
Mood changes	0	07(25%)	-
Mastalgia	2 (6.7%)	06 (21.4%)	0.272
Leucorrhoea	6 (20%)	5 (17.8%)	1.000

[Table/Fig-6]: Comparison of patient satisfaction parameters and side effect profile between groups.

improving trend towards Ideal bleed (IB) pattern in subsequent cycles in both the groups. IB pattern in Cycle2 and Cycle3 was significantly higher compared to Cycle1 in Nuvaring and OCP groups (p-value =0.0057, < 0.001 respectively). Incidence of Ideal bleed (IB) was slightly higher for Nuvaring than OCP in all 3 cycles, although no statistically significant difference was there between groups (p-value= 0.286) [Table/Fig-5]. Similarly the incidence of late withdrawal (LB) bleed was lower in Nuvaring than the OCP, however no significant difference was observed between groups (p-value=0.752). There was a decreasing trend of LB in subsequent cycle in both the groups. Breakthrough bleed was higher in all cycle of OCP group ranging from, 7%-14%, whereas only 1/ 30 women reported breakthrough bleed in Nuvaring group in cycle 3.

[Table/Fig-6] shows that more number of women in Nuvaring group were satisfied with treatment (29/30) and recommended its usage as compared to OCP group (23/28); however the difference in number was not statistically significant. Compliance was better in Nuvaring group; because of once-a-month insertion, all women completed the study compared to 28 women in OCP group. 8/28 women (28%) discontinued in OCP group after 3 month of therapy, main reason being poor compliance and breakthrough bleed where as 3/30 women (10%) in Nuvaring discontinued and reason being persistence of dysmenorrhea. No major side effects were encountered during 3 month therapy in any of the group; however minor side effects were seen more in OCP users; but the difference was not significant statistically. Two cases of Nuvaring expulsion was reported, however no coital difficulty or irritation was reported by user or her partner.

[Table/Fig-7] Persistent severe dysmenorrhoea was seen in 7% of Nuvaring and 3.5% of OCP group after 3 month of therapy, whereas persistent mild to moderate dysmenorrhoea was seen in 23.3% of Nuvaring and 10.7% of OCP users. No significant change from baseline values was found in haemoglobin level and body weight at the end of study period in both groups [Table/Fig-8].

Variables	Nuvaring		OCP		p- value (Inter group)
	Pre	Post	Pre	Post	
No dysmenorrhoea	16 (53.3%)	21 (70%)	18 (64%)	24 (85%)	0.38
Mild-Mod dysmenorrhoea	9 (30%)	7 (23.3%)	4 (14.2%)	3 (10.7%)	
Severe dysmenorrhoea	5 (17%)	2 (7%)	6 (21.4%)	1 (3.5%)	
p-value (Within group)		0.018		0.046	

[Table/Fig-7]: Effect of drugs on dysmenorrheal.

Variable	Group	Pre therapy	Post thepary	Difference (Pre –post) (95% CI)	p-value
Haemoglobin (gm/dl)	Nuvaring	10.77± 1.42	10.88± 1.48	-0.1167 (-0.593,-0.359)	0.620
	OCP	10.15± 1.66	10.73± 1.50	-0.339 (-0.869, -0.1905)	0.200
Weight (kg)	Nuvaring	56.37± 12.60	56.80± 10.82	-0.433 (- 2.203,-1.336)	0.620
	OCP	57.18± 9.254	57.89± 9.24	-0.714 (-1.903, -0.474)	0.228

[Table/Fig-8]:] Effect of drugs on hemoglobin and weight.

DISCUSSION

Nuvaring has been found comparable to OCPs for contraception usage. Nuvaring may be the contraceptive of choice in patients who wish to avoid inconvenience of daily pill intake, those with busy schedule and frequent travelling. Because of vaginal route of administration, it allows steady and continuous release of hormone, resulting in stable serum concentration. This is responsible for good cycle control and less systemic side effects [7,8]. It is one of the best contraceptives for women suffering from AUB. The return of ovulation after stopping Nuvaring usage is generally in 3-4 weeks and it does not cause long term infertility. Various treatments for AUB include tranexamic acid, progestogen only pills, OCPs, GnRH analogues etc, depending on the patient profile. Earlier only the oral route was available but now with the advent of new technology, other options like parenteral, subdermal, nasal, and intravaginal route are also available.

In the present study, PBAC score improved from baseline score of 214.87±86.29 to 87±42.29 in Nuvaring group and 237.57±86.29 to 74.75±51.58 in OCP group after the completion of 3 month therapy. Both Nuvaring and OCP were found to significantly reduce menstrual blood loss within group; however no significant difference was found when PBAC score reduction was compared between groups. Incidence of ideal bleed in each cycles were higher in Nuvaring group compared to OCP group, which provides evidence that cycle control was better with Nuvaring group. Besides good cycle control and decrease in PBAC score, break through bleeding was noticed only in one cycle out of total 90 exposed cycles in Nuvaring user, compare to 10 cycles of 84 exposed cycles in OCP

group. This observed low incidence of breakthrough bleed and good cycle control with Nuvaring was earlier reported by Milsom et al., Roumen et al., Oddsson et al., Ahrendt et al., [7,9-11]. Low incidence of breakthrough bleed with Nuvaring may be explained by its continuous, steady and precise dosing, resulting in stable serum concentration [1,4].

OCP have been widely prescribed for treatment of dysmenorrhoea and chronic pelvic pain. However literature shows conflicting reports. Vercellini et al., & French in 2005 in their study reported significant decrease in dysmenorrhea in OCP user. Whereas Proctor et al., found evidence insufficient to conclude on effectiveness of OCP in treating dysmenorrhoea [12-14]. In our study, 47% women in Nuvaring and 35.6% women OCP group reported dysmenorrhoea at start of study. Post 3 month therapy, dysmenorrhoea was seen in 30.3% of Nuvaring and 10.5% of OCP group. Thus both the drugs were found to be effective in treating dysmenorrhoea with OCP being superior, although difference was not significant statistically. In present study no major hormone related side effects was seen, where as minor side effects such as headache, GI upset were seen in both groups. Nausea was commonly encountered minor side effect in OCP group; Six out of 28 women reported nausea in OCP group, compare to none in Nuvaring group. Similarly mood swings were reported only in OCP user; 25% women in OCP group complained of mood swings while on therapy compared to none in Nuvaring group. Incidence of headache was also higher in OCP group compared to Nuvaring group. 14% women in OCP group complained of headache compared to 6% in Nuvaring group, however difference was not significant statistically. An open label, non comparative study reported 5.8% headache in Nuvaring user, which was similar to our study [8]. Two women in Nuvaring group complained of expulsion of ring. No coital dysfunction was reported in Nuvaring user. No significant changes in body weight and haemoglobin level were found in both groups as an effect of hormone therapy. Current trial found Nuvaring to be as effective as OCP for treating AUB in carefully selected patients, though sample size and short duration of study were limiting factors.

CONCLUSION

Present study shows Nuvaring to be as effective as OCP for symptom control in abnormal uterine bleeding. Side effects were minor, few and high rates of patient satisfaction were observed. The convenience of once- a- month administration motivated majority of patients to continue therapy even after the study period, for dual benefit of contraception as well as AUB treatment. Dysmenorrhoea was relieved more in OCP users, though difference was not statistically significant.

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