

Mirena and NuvaRing in Management in Dysfunctional Uterine Bleeding

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ABSTRACT

Introduction: Abnormal uterine bleeding in reproductive age group is one of the commonest gynecological problems in women. Ovulatory dysfunction is one of the commonest causes of AUB. Combined oral contraceptive pills and oral progesterone are used as first line treatment of ovulatory dysfunction. However many women may not be desirous of oral medication. In such circumstances keeping in view of patient preferences and her medical condition, vaginal rings and intrauterine devices containing hormonal preparations may be a preferable.

Material and Methods: Two groups including 80 women in each group who were fulfilling the inclusion criteria were selected. In one group NuvaRing which releases 15µg ethinyl estradiol and 120µg etonogesterol daily and requires intravaginal monthly insertion and in the other group of patients Mirena which is a intrauterine device with levonogestrol was inserted. Both groups were followed up for 4 months. The efficacy and side effects were measured in terms of change menstrual cycle pattern and Primary Outcome Pictorial Blood Loss Assessment chart (PBAC) score. Other parameters included side effects and acceptability of the device used. Data was analyzed by statistical software SPSS 21.0.

Results: NuvaRing and Mirena were offered to women in reproductive age group for management of dysfunctional uterine bleeding which resulted in significant symptomatic improvement, and a statistically significant decline in PBAC score. These women also had an increase in hemoglobin levels and improved feeling of wellbeing.

Conclusion: Both NuvaRing and Mirena can be used for management of abnormal uterine bleeding. The initial response to symptomatic improvement in terms of PBAC score was better with NuvaRing but in the final outcome both are comparable.

Keywords: Mirena, NuvaRing, Dysfunctional Uterine Bleeding

rate of 53 per thousand women. Abnormal uterine bleeding due to ovulatory dysfunction reflects a disruption in the normal cyclic pattern of ovulatory hormonal stimulation to the endometrial lining. The bleeding is irregular and unpredictable. The pattern may vary from being excessively heavy or light and may be prolonged, frequent, or random. The ovulatory dysfunction bleeding is mainly because of an ovulatory cycles (90%).

The pathophysiology involves unopposed estrogen stimulation of endometrium in anovulatory cycles, which leads to thickened endometrium that soon out grows the blood supply. This leads to sloughing of endometrium due to ischemic necrosis. The bleeding that ensues may be heavy and prolonged and irregular. Subsequent healing of the endometrium is also affected. PCOD, hypothyroidism are common etiological factors.⁵

Ovulatory bleeding in contrast to the above is due to irregular shedding of the endometrium. Both sub threshold levels and very high estrogen levels have been implicated. It may occur in patients with PCOD and endometriosis. The bleeding is mostly heavy and regular. With the advent of newer and better hormones available in lower doses, which can be administered through other routes of administration than the oral route, the management of anovulatory bleeding, has evolved leading to reduction in side effects and better patient compliance. Treatment can now be individualized and the management of AUB now not only encompasses treatment of AUB but also takes into consideration the patient's choice, her contraceptive needs and desire to retain infertility in order to achieve improved quality of life.

Till recently combined oral contraceptives and oral progesterones were used but now combined intravaginal ring (NuvaRing) and intrauterine devices containing progesterone (Mirena) are being increasingly used for management of AUB. Both of these have devices are acceptable and effective. A

INTRODUCTION

Abnormal uterine bleeding is a common distressing gynecological symptom comprising of 7-14% of the gynecological OPD and is not only causes physical and psychological discomfort but also has profound detrimental effect on health status and quality of life.^{1,2} Ovulatory dysfunction is one of the commonest causes of AUB. Anovulation is more common accounting for more than 90% of the cases. Combined oral contraceptive pills and oral progesterone are used as first line treatment of ovulatory dysfunction.³ The prevalence rate in India is 17.9%.⁴ A United States population-based survey of women aged 18-50 years in November 2017 reported an annual prevalence

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distinct advantage of these devices is that the bioavailability of drugs is good due to avoidance of gastrointestinal absorption and hepatic first-pass metabolism. Patient compliance is also better because of reduced administration. NuvaRing® is combined contraceptive hormonal ring made of copolymer evatane. It is soft and flexible and transparent in appearance. The diameter of the ring is 55mm and thickness is 4mm. It is applied intravaginally and is for once-a-month application. It releases 15µg Ethinyl Estradiol (EE) and 120µg etonogestrel per day. The mechanism of action is similar to oral contraceptives at a much smaller dose with an added convenience of monthly application. It acts by ovulation suppression. Studies and clinical trials have revealed that Nuvaring not only controls AUB but also has good contraceptive efficacy. The patient compliance is also better compared to the other modalities.

Mirena is a hormonal intrauterine device that has T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel around the vertical stem. The hormone is released initially at a rate of 20 µg/day that later reduces to a rate of 14 µg after 5 years, which is still in the therapeutic range.^{6,7} In addition to hormonal action, it also causes foreign body reaction. LNG IS a 19-nortestosterone derivative. The strong progestational effect makes the endometrium, atrophic and inactive, although ovulation is usually not suppressed. The evaluation of blood loss and the definition of amenorrhoea, complete inhibition of menstruation has been observed in 20–60% of LNG-IUS users (Levonorgestrel Intrauterine System). The aim of the present study was to evaluate the efficacy, acceptability and drawbacks of NuvaRing and Mirena in management of abnormal uterine bleeding.

MATERIAL AND METHODS

This study was carried out in the Department of Obstetrics and Gynecology Army College of Medical Sciences, New Delhi from June 2017 till December 2017. Eighty patients were included who met the inclusion criteria and patients consent was taken. They were informed about the study and its content. All patients were given a check proforma and their details, which included history, examination and investigation, were recorded.

Inclusion criteria were as follows:

1. Age group of 20 to 40yrs, sexually active
2. No known medical disorder such as diabetes mellitus, hypertension, infection, malignancy etc
3. No organic pathology of genital tract
4. Not desirous for pregnancy for at least 1 year duration

Nature of the study was double blind randomized control study. Eighty patients met the inclusion criteria and they were informed in details about the study and its content. All patients were given a check proforma and their details, which included history, examination and investigation, were recorded. An informed consent was obtained from all the patients. Patients were free to leave the study at any point of time without assigning any reason and without their treatment being affected. They were randomized into two groups (1:1 ratio) based on computer generated random number table by the statistician. One group comprising of 40 women were given NuvaRing therapy for 4 months and the second group was given Mirena intrauterine device for the same period. The NuvaRing insertion and removal was initially done by the doctor and patient was explained and demonstrated the procedure initially on the patient herself. It was inserted on the fifth day of the cycle and removed after three weeks for one week. It was during this week that withdrawal bleeding occurred. A new ring was inserted after one week of ring free period. Mirena was inserted as an OPD procedure post menstrually. Follow up was done initially after a week and thereafter every month. Record of menstrual pattern and associated side effects maintained by the patient was used for following up the patient. Pictorial Blood loss Assessment Chart was used to assess the amount of blood loss in each cycle. Other parameters such as weight and haemoglobin records were also maintained.

STATISTICAL ANALYSIS

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Chi-square test, Independent samples 't'-test and Fisher exact test were used to compare the data. 'p' value less than 0.05 was considered as statistically significant.

RESULTS

Results are summarized in table 1. Mean age of patients In Mirena and NuvaRing groups was 33.28 ± 3.49 and 32.8 ± 3.66 years. Parity of patients ranged from P1 to P3, majority of patients in both the groups were para 2(60% and 55%

Sr No.	Characteristic	Mirena (n=40)	NuvaRing (n=40)	Statistical significance 'p' value (Independent samples 't'-test)
1.	Mean Age±SD (years)	33.28±3.49	32.48±3.66	0.320
2.	Parity			0.691 ^a
	P1	10 (25.0%)	9 (22.5%)	
	P2	24 (60.0%)	22 (55.0%)	
	P3	6 (15.0%)	9 (22.5%)	
3.	Mean Haemoglobin level±SD (g/dl)	9.84±0.66	9.79±0.71	0.720
4.	Mean body weight±SD (kg)	59.18±4.41	58.40±5.30	0.479
5.	Mean PBAC score±SD	199.45±30.23	224.35±48.94	0.008

^aChi-square test

Table-1: Comparison of Baseline characteristics of patients in two groups

SN	Characteristic	Mirena (n=40)		NuvaRing (n=40)		Statistical significance 'p' value (Independent samples 't'-test)
		n	Mean±SD	n	Mean±SD	
1.	At enrolment	40	199.45±30.23	40	224.35±48.94	0.008
2.	Cycle 1	37	164.81±33.42	40	136.50±58.63	0.009
3.	Cycle 2	36	120.67±32.64	40	106.20±45.64	0.120
4.	Cycle 3	34	86.29±24.60	40	86.13±40.79	0.983
5.	Cycle 4	33	53.18±14.73	39	60.54±11.72	0.021

Table-2: Evaluation of PBAC at different follow up intervals

Sr No	Characteristic	Mirena (n=40)		NuvaRing (n=40)		Statistical significance 'p' value (Independent samples 't'-test)
		n	Mean±SD	N	Mean±SD	
1.	Mean PBAC±SD after 3 cycles	33	53.18±14.73	40	60.54±11.72	0.021
2.	Mean Hb±SD	36	10.03±0.59	40	10.17±0.75	0.358
3.	Mean Change in PBAC±SD	34	-142.85±32.07	39	-161.10±45.68	0.058
4.	Mean Change in Hb±SD	36	0.22±0.29	40	0.38±0.49	0.093
5.	No. of expiries	3 (7.5%)		0		0.279 ^a
6.	No. of drop-outs	3 (7.5%)		1 (2.5%)		0.615 ^a
7.	Expiries/Drop-outs	6 (15%)		1 (2.5%)		0.108 ^a

^aFisher exact test

Table-3: Final Outcome

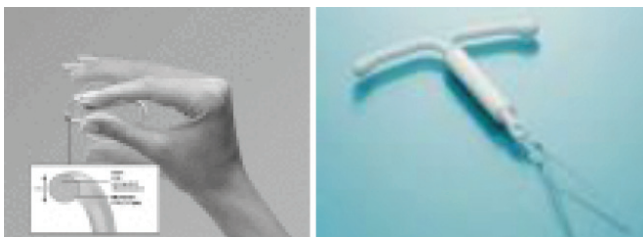


Figure-1: Combined contraceptive vaginal ring (NuvaRing®) and Mirena

respectively). Mean haemoglobin levels were 9.84±0.66 and 9.79±0.71 g/dl respectively in Mirena and NuvaRing groups respectively. Mean body weight was 59.18±4.41 and 58.40±5.30 kg respectively in Mirena and NuvaRing groups respectively while mean PBAC score was 199.45±30.23 in Mirena and 224.35±48.94 in NuvaRing group respectively. Statistically, there was no significant difference between two groups with respect to all the baseline characteristics except for PBAC score that was significantly higher in NuvaRing group as compared to that in Mirena group (p=0.008).

Table 2 summarizes PBAC scores at different follow up intervals. A baseline, cycle 1, cycle 2, cycle 3 and cycle 4 intervals mean PBAC score was 199.45±30.23, 164.81±33.42, 120.67±32.64, 86.29±24.60 and 53.18±14.73 respectively in Mirena group and 224.35±48.94, 136.50±58.63, 106.20±45.64, 86.13±40.79 and 60.54±11.72 respectively in NuvaRing group. Statistically, mean PBAC was lower in NuvaRing group as compared to that in Mirena group at Cycle 1 interval while it was lower in Mirena group as compared to NuvaRing at enrolment and at Cycle 4 intervals respectively (p<0.05).

Table 3 summarizes the final outcome of parameters in both the groups. After 4 cycles and at final follow-up, mean PBAC scores and Hb values were 53.18±14.73 and 10.03±0.59 g/

dl respectively in Mirena group whereas in NuvaRing group they were 60.54±11.72 and 10.17±0.75 g/dl respectively. Statistically, there was a significant difference between two groups for mean PBAC scores, which were significantly lower in Mirena as compared to NuvaRing group (p=0.021). Although, mean reduction in PBAC was significantly higher in NuvaRing group (161.10±45.68) as compared to that in Mirena group (142.85±32.07) yet this difference was not significant statistically (p=0.058). An increase in mean haemoglobin level was observed in both the groups but there was no significant difference between two groups (p=0.093). There were 6 expulsions/drop-outs (3 expulsions and 3 drop outs) in Mirena group as compared to only one drop out in NuvaRing group, but this difference was not significant statistically (p=0.108).

DISCUSSION

Abnormal uterine bleeding has a high prevalence in women of reproductive age group. Heavy bleeding during menstrual cycle is often incapacitating and often leads to anaemia if not managed. In the past oral contraceptives and oral progesterones were being used, but now with advent of intrauterine devices and vaginal ring delivery systems the management and compliance has improved.

This study on Mirena(Lng-IUS) and NuvaRing (intravaginal combined contraceptive (CCVR), NuvaRing®, Organon Int., Oss, The Netherlands) on management abnormal uterine bleeding was done in terms of PBAC scores, improvement in hemoglobin status, acceptability and side effects. It was a randomized control study and patients between twenty to forty years were selected.

The PBAC scores in the Mirena group reduced from a mean value of 199.45 to 53.18 after completion of four month therapy and in the NuvaRing group reduced from 224.35 to 60.75. Both groups showed improvement which was

swifter in NuvaRing group as compared to Mirena group. The hemoglobin rise was however almost similar in both groups. The breakthrough bleeding was more in Mirena users compared to those of NuvaRing. The acceptability in NuvaRing was slightly more because of ideal bleeding pattern. The expulsion in Mirena was observed in three patients. The disproportion between the length of uterine cavity size and IUD could have been the cause of expulsion the consequences of a disproportion between IUD size and the uterine cavity have been analysed by several authors. Expulsion rate observed in previous studies on Mirena using patients was observed to be 2.9% when it was used only for contraceptive purposes. This increased significantly if medical causes such as endometriosis, pain and fibroids were present to 10%-13%. Both groups by the end of the observed period of therapy had significant reduction of PBAC scores and symptomatic improvement in abnormal uterine bleeding. None of the patients conceived during the observed period in either group. Similar observations have been made during Randomized control trials done by Jain Set al.⁸, They observed significant improvement in reduction of blood loss in menstrual cycle and ideal bleeding pattern was observed with NuvaRing. Breakthrough bleeding was also minimal in their study patients. Large non-comparative multi-center registration studies and in daily clinical practice Roumen et al 2006 found good cycle control, tolerability and acceptability with NuvaRing besides good contraceptive efficacy.⁹ Breakthrough bleeding was more with Mirena than NuvaRing was because of stable serum concentration obtained due to steady and continuous precise dosing.⁹⁻¹² Milsom et al also reported very low evidence of breakthrough bleeding and high incidence of good cycle control with NuvaRing.¹²⁻¹⁶

Minimal side effects such as nausea, bloating sensation were observed in NuvaRing group. Vaginitis was observed in less than 1% patients. In our study only one patient had vaginitis. Pallavi C et al.²⁶ studied effects of Mirena in abnormal uterine bleeding and after 4 four months of therapy found significant decrease to the extent of eighty percent and an appreciable increase in hemoglobin status. Results of this study are similar to other studies done in the past.¹⁷⁻²⁵ Slightly less acceptance of Mirena compared to NuvaRing was primarily because intermittent spotting and expulsion. Similar reasons for dropout were reported in aforementioned study by Pallavi C et al.²⁶ The findings of present study thus showed that although both the treatments offered symptomatic improvement, however, the decline in PBAC was swifter in NuvaRing as compared to Mirena group but in the final evaluation, both groups were comparable.

CONCLUSION

Both NuvaRing and Mirena are effective in management of abnormal uterine bleeding. Both treatments offer good symptomatic improvement, however, the decline in PBAC was swifter with NuvaRing as compared to Mirena group but in final evaluation, both groups were comparable. Both had good acceptability and contraceptive efficacy and improve

the quality of life of the patient. Side effects of both are minimal and compliance rate is improved.

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