CONTRACEPTION WITH MEDICATED INTRAVAGINAL RINGS

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SUMMARY

Sixty nine women were given Contraceptive Vaginal Rings (CVR) impregnated with hormones in two dosage schedule. Group I - 20 cases received CVR containing dnogestrel 71-137 mg and estradiol 34-65 mg from Feb. 1979 Jan. 1980, Group II - 49 women were given CVR impregnated with Levonorgestrel 110-120 mg and estradiol 65-74 mg between June to Dec.1984. The treatment was planned to cover six cycles in group I and 12 cycles in group II. The contraceptive rings were used for 3 weeks in each month (from day 5-25 of menstrual cycles) and the treatment covered 258 cycles.

Continuation rate at six months was slightly better (71.4%) in group II as compared to group I (65%). There was no difference in menstrual pattern of both the groups. One pregnancy in each group was reported giving an overall incidence of 9.3/100 women year of exposure. Endometrial biopsies were attempted in 6 cases (group I) and 16 subjects (group II) in premenstrual phase. Ovulation was found to be suppressed in 86%. One case showed benign cystic glandular hyperplasia of the endometrium in group II. Radio Immuno assay (Progesterone and Estradiol) was carried out in five women (groupI) which showed suppression of ovulation in three in first treatment cycle and return of ovulation in one at fifth months of treatment.

INTRODUCTIONS

Various hormones have been widely used for fertility regulation, but an ideal contraceptive with suitable dosages has yet to be discovered and the search is still on for a simple, effective, safe, reversible and inexpensive methods.

Contraceptive vaginal rings (CVR) contain steroids which are released slowly from a reservoir and absorbed through the vaginal mucosa. Contraceptive effect is attained by inhibition of ovulation. A number of

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studies have given promising result with this method (Mishell et al, 1970,1979 and Tovienen et al, 1978). Two WHO Multicentre Clinical Trial (1974-75 and 1976-77) have also proved the efficacy of this method. Recently results on global Multicentre trial indicated effectiveness and continution rates of CVR equal to that of oral contraceptive. In view of these findings, the present study was undertaken in 69 women to evaluate the contraceptive efficacy, acceptability and safety of Intravaginal rings impregnated with hormones in two different dosages schedules.

MATERIALS AND METHODS

Sixty nine women aged 20/35 years with parity 1-4 participated in this study. The trial was carried out under HRRC (I.C.M.R.) at K.G's Medical College, Lucknow. These cases were divided into two groups.

GROUP I- (20 cases)

Twenty cases received CVR containing d-norgestrel (71-137 mg) and estradiol (34-65 mg) from Feb. 1979 to Jan. 1980. The outer diameter of the ring was 55 mm and internal diameter 40 mm.

GROUP II- (49 cases)

Forty nine women were given CVR impregnated with Levonorgestrel (110-120 mg) and estradiol (65-74 mg) between June to Dec. 1984. These are cylindrical Contraceptive Vaginal Rings of polysiloxane fabricated in a 3 layered shell design having an outer diameter of 58 mm and thickness 9 mm.

The subjects were instructed to insert ring in vagina on day five of the menstrual cycle and thereafter to remove it after three weeks in each month. The treatment was planned to cover six cycles in Group I and 12 cycles in Group II, as the effect of the each ring was supposed to last for this period of time.

Routine investigations like Haemoglobin estimation, Blood pressure and weight recording, urine analysis and cytological examination were done prior to the insertion of the rings and subsequently repeated after three and six months. In five cases of Group I, peripheral blood samples were collected in first and fifth treatment cycles on eight, fourteenth and twenty fourth day of the menstrual cycles. Plasma levels of Progesterone and Estradiol were determined by Radio-immuno assay (procedure by reagents and methods provided by World Health Organisation under their matched reagents programme (1979).

OBSERVATIONS AND RESULTS

Sixty nine subjects received CVRs for 258 cycles and were analysed

Side Effects :

The commonest side effect in both the groups of CVR users were increased vaginal discharge, pain (abdominal, back or body) and weight gain. Of the total 13 (19 %) cases who suffered from vaginitis, 15% were suffering from monilial infection. Incidence of dyspareunia was higher 10.2 % (5 out of 49 cases in group II as compared to group I (5%). One case in group II developed jaundice after second cycle (? Viral hepatitis) necessitating the removal of the ring.

Menstrual pattern :

There was no difference in menstrual pattern of both the groups. Cycles were normal in 71 % of cases. Two cases in group II required removal because of heavy bleeding and amenorrhoea. None of the cases required removal due to menstrual abnormality in group I.

TABLE I

Side effects in contraceptive vaginal ring users

Sr. No. Side Effect	Group I (20)		Group II (49)		Total (69)	
	No.	%	No.	%	No.	%
1.Excessive vaginal discharge	5	25.0	8	16.3	13	18.8
2.Abd. pain/Backache or bodyache	3	15.0	8	16.3	11	16.0
3.Weight gain (2.6 kg)	3	15.0	5	10.2	8	11.6
4.Weakness/dullness	3	15.0	3	6.1	6	8.7
5.Nausea	3	15.0	1	2.0	4	5.8
6.Dizziness	2	10.0	1	2.0	3	4.3
7.Dysparunia	1	5.0	5	10.2	6	8.7
8.Headache	1	5.0	1	2.0	2	2.9
9.Increased appetite	1	5.0	1	2.0	2	2.9
10.Leg pain	1	5.0	1	4.1	2	2.9
11.Urinary discomfort	–	–	2	4.1	2	2.9
12.Itching all over the body	–	–	2	4.1	2	2.9
13.Eye pain	–	–	1	2.0	1	1.4

TABLE II

Menstrual pattern in contraceptive vaginal ring users

Menstrual Pattern	Group I (96)		Group II (162)		Total cycle (258)	
	No.	%	No.	%	No.	%
Normal cycles	68	70.8	115	71.0	183	70.9
Scanty periods	17	17.7	30	18.5	47	18.2
Short cycles	5	5.2	8	4.9	13	5.0
Amenorrhoea	4	4.2	2	1.2	6	2.3
Prolonged duration or bleeding	1	1.0	3	1.8	4	1.6
Long cycles	1	1.0	–	–	1	0.4
Heavy period	–	–	4	2.5	4	1.6
B.T.B.	3	3.1	5	3.1	8	3.1

TABLE III

Endometrial biopsy in contraceptive vaginal ring users

Biopsy	Group I (20)	Group II (49)
Number	6	16
Cycle	1,5,6	1,2,3,4,6
Phase	Premenstrual	Premenstrual
H.P.R.	-- No tissue - 5	-- No tissue - 5
	-- N.E. with chronic - 1	-- Scanty tissue - 3
	Cervicitis and	(on opinion)
	adenomatus polyp.-- N.E.	- 4
		-- S.E. - 3
		-- Benign cystic - 1
		Hyperplasia

N.E. : Non-Secretory Endometrium * S.E. : Secretory Endometrium,
H.P.R. : Histopathological report.

TABLE IV

Reasons for discontiniuation of contraceptive rings

Reasons	Group I (20)		Group II (49)		Total (69)	
	No	%	No.	%	No.	%
Time completed or study terminated	13	65.0	35	71.4	48	71.0
Expulsion	4	20.0	4	8.2	8	11.6
Side effect	2	10.0	5	10.2	7	10.1
Pregnancy	1	12.5*	1	7.4	2	9.3*
Botheration	–	–	2	4.1	2	2.9
Transferred	–	–	2	4.1	2	4.4

*Per 100 women years of exposure

Endometrial Biopsy

Endometrial biopsies had been attempted in 6 cases (group I) and in 16 cases (Group II) in premenstrual phase. In group I all cases showed anovulationj. Of these one case also showed ademomatous polyp with chronic cervicitis. In three women uterus became smaller in size and in other case there was enlargement of the ovary at the close of the therapy. In group II, out of 16,13 cases showed anovulation (in 3rd to 6th cycles) and 3 subjects showed secretory endometrium in first treatment cycle. Of the 13 women showing anovulation, one case had polymenorrhagia, endometrial biopsy report in 4th cycle was benign cystic glandular hyperplasia.

None of the cases showed any sign of cervical dysplasia on cytological exmamination.

Reasons for discontinuation

Reasons for dropout were more or less same in both the groups, though continuation rate at the end of six months was slightly better in group II.

Thirteen women (65%) in group I continued to use rings for six months as planned while in group II, 35 (71.4%) wanted to continue with CVR but the study was terminated. Expulsion was responsible for dropouts in 4 cases in each group. Two cases (Group II) had stopped using the ring because of botheration. Only one woman, conceived in each group after third and fourth cycle with ring in situ giving a comined pregnancy rate of 9.3/100 women years of exposure. Both women had suction evacuation followed by the insertion of IUD.

Radio-immuno assey

Pre treatment hormone levels (progesterone and Estradiol) were determined in 5 women in group I. Progesterone values ranged from 10.39 - 51.03 n mol/1 and estradiol levels 469.70 - 2288.53 p mol/1 in mid cycle phase. In first post treatment cycle 3 out of 4 subjects showed suppression of ovulation as the progesterone levels were below 10.00 n mol/1 during mid menstrual cycle. Evidence of ovulation was found in two cases in fifth

TABLE V

Hormonal assay in intravaginal rings users

Group	No. of cases	Phase of menstrual cycle						Ovulation
		Proliferative		Mid cycle		Secretary		
		Estra-diol p mol/l	Proge-sterone n mol/l	Estra-diol p mol/l	Proge-sterone n mol/l	Estra-diol p mol/l	Proge-sterone n mol/l	
I. Pre treatment (Control)	5	605.72	4.33	1299.95	20.57	321.37	43.87	Present
II. Post treatment								
(a) First cycle	4	662.48	6.35	1632.59	9.71	719.37	15.16	Suppressed in three
(b) First Cycle	2	229.68	5.65	787.28	13.03	304.07	29.23	Present

treatment cycles. One case who earlier showed suppression of ovulation, it was found have occurred in the fifth month, this was also confirmed by cytohormonal evaluation of vaginal smear of these cases.

DISCUSSION

The medicated vaginal devices aim to provide continuous protection against pregnancy over for at least three months, depending upon the release rate and the types of steroid contained in them Contraceptive rings either inhibit the ovulation or have an antifertility effect by their actions on the cervical mucus, endometrium or fallopain tubes.

Results of second WHO Multricentre Trial (1976-77),1978 showed high degree of inhibition of ovulation (58%) and menstrual irregularity (58% oc cycles). In Toivonen et al's series (1979) 20 women used contraceptive rings impregnated with Levonorgestrel (97-140 mg) and Estradiol (46-66 mg) for six months. Continuation rate was 90% at six months. Commonest side effects were weight gain in 4 (20%), oedema, headache, monilial vaginitis and urinary discomfort were reported in one each subject (5%). Expulsion was seen in 1 (5%). Only 3 (15%) women had regular withdrawl bleeding. Radio-immuno assay showed only mild suppression of pitutary. In present series overall continuation rate was 71% at six months. Commonest side effects were excessive vaginal discharge in 19% (of these 15% monilial infection), pain in 16% and weight gain of 2-6 kg in 12%. Incidence of dyspareunia was high 10% and with Levonorgestrel CVRs (group II) as compare to d- norgestrel CVRs (group I) where it was only 5%. This could be due to hard texture or larger outer diameter of Levonorgestrel CVR. Expulsion rate was higher in this series (12%) as compared to 3% reported by Toivonen et al's series (1979). Menstrual abnormality in this study was only 30% of cycles comparatively less as reported in WHO Multicentre Trial (1976-77).

Contraceptive vaginal rings impregnated with hormone appear to be a good method of fertility control especially in our country where 80% of the population live in rural area and in whom it is difficult to inculcate the habit of regular pill taking. It can be inserted and removed by the users with only elementary instruction from an auxiliary health or social worker. At present clinical trials with CVRs terminated by the ICMR as the Centre for Biomedical Research, of population Council, New York, USA shows excessive endometrial decidualization in both rabbits and monkeys.

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