A CLINICAL STUDY OF ACCEPTABILITY OF DIFFERENT DELIVERY SYSTEMS OF HORMONAL CONTRACEPTIVES

by

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Summary

895 women were studied for acceptibility of different hormonal contraceptives. 652 cases had different types of oral pills, 153 had long-acting injectable preparations, 70 had subdermal silastic implants and 20 had intravaginal rings. Follow-up was possible in 747 cases. Side-effects were responsible for discontinuation in 318 of 747 cases. Initial acceptability was high. At the end of 24 months the continuation rate for 'Pills' was only 1.9%. The rates for monthly injection and subdermal implants were 4% and 12.8% respectively.

Introduction

A major advance in the field of fertility control came with the discovery of the oral progestogens. Though widely used in many parts of the world, undesirable side effects caused by these drugs have been the major reasons for continuing research in this field. In our country there is special need to investigate the safety of these pills because many women to whom they will be administered are likely to be anaemic, hypoproteinemic or may have suffered from amoebic hepatitis at some time or other. Another major drawback of oral contraceptive is the need for continuous motivation to ensure regular pill taking and their unsuitability in the first six months of lactation. Long acting injectable preparations, subdermal implants and intravaginal rings are some of the methods advocated to overcome this handicap. Mishell *et al* (1978) and Toivonen *et al* (1978) have published encouraging results for hormone impregnated vaginal rings and two WHO Multicertric Clinical Trials (1974-75 and 1976-77) have also proved the efficacy of this method. This study deals with our experience in the field of hormonal contraception in the Contraceptive Teasting Unit, Queen Mary's Hospital, Lucknow from October 1967-January 1980.

Material and Methods

Eight hundred niney-five women attending the Family Planning Clinic of Queen Mary's Hospital, were registered for the present study and comprised of the following 4 groups:

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		Total No. of cases	No. followed
GROUP I;	ORAL PILLS (652 cases) Three types of pills were used:		
	(A) Ovulen (Ethinodiol diacetate 1 mg. + Mestranol 0.1 mg.) taken cyclically from day 5-25.	360	300
	(B) Mini Pill (Chlormadinone acetate 0.5 mg.) given without interruption throughout cycle.	192	122
	(C) Once-a-month pill (Quingestanol acetate 2.5 mg. + Quinestrol 2.0 mg.) first pill given on day 2 of menstrual period, second pill after 3 weeks and subsequent pills monthly on the same calendar date.	100	96
GROUP II:	LONG-ACTING INJECTABLE PREPARATIONS (153 cases)		
	(A) Depo-medroxy progesterone Acetate (DMPA)—85 cases in 2 dosage schedules:		
	(i) 150 mg. I.M. three monthly (including 10 postpartum cases)	60	46
	(ii) 25 mg. I.M. monthly with one tablet of 0.5 mg. Quinestrol acetate orally.	25	25
	(B) Norethisterone Enanthate (NET-OEN)—68 cases also in 2 dosage schedules:		
	(i) 200 mg. I.M. three monthly	34	34
	(ii) 20 mg. I.M. monthly	34	34
GROUP III:	SUBDERMAL SILASTIC IMPLANTS (70 cases) (Inserted on lateral aspect of thigh under local anaesthesia. Action of implant expected to last for one year).		
	(A) Norethindrone rods (65 mg.)	50	50
	(B) Norethindrone Acetate Capsules (99 mg.)	20	20

		Total No. of cases	No. followed
GROUP IV:	INTRAVAGINAL RINGS (20 cases) (Impregnated with d-noregestrel in doses varying from 71-131 mg. + oestradiol 34-65 mg. inserted in vagina on day 5 and retained till day 25 of each cycle. One ring usable for six months).	20	20

All the subjects in the study were in the age group of 16-40 years, with 90% in the age group of 25-30 years and with parities ranging from 0-14, of which 86% were para 1-6. In all cases after a careful history, general and pelvic examination was carried out. Haemoglobin estimation, weight recording, urine analysis and cytological examination were done in every case before starting drug and repeated during therapy at three or six monthly intervals.

Observations and Results

Follow-up was possible in 747 cases (83.5%), of which 10 postpartum cases were analysed separately. The period of use for pills ranged from 31-60 months, for injectables from 1-42 months, for implants, 3-24 months and with intravaginal rings 2-6 months.

Side Effects

Various side effects were encountered with all formulations, the commonest being menstrual abnormalities and G.I.T. symptoms but only those which were responsible for dropout are listed and shown in Table I.

Menstrual abnormalities, were seen with all formulations and ranged from B.T.B. (Break through bleeding) to menorrhagia, oligomenorrhoea and even amenorrhoea. Discontinuation on account of menstrual abnormalities was highest in the group getting three monthly injections of either DMPA or NET-OEN (50-66.7%) and lowest in cyclical pill users (10.0%). The commonest abnormality with minipills was B.T.B. Amenorrhoea and menorrhagia were frequent with three monthly injectables and least with implants and vaginal rings. Post pill amenorrhoea was seen in only 2 cases.

It will be noticed that G.I. tract symptoms were commonest with oral pills, the highest incidence being with the 'pill-a-month' (30.2%), least with minipills (10.7%) and 16.3% with pills cyclically administered. Only one woman getting monthly injections of DMPA alongwith quinestrol complained of nausea, vomiting. None of the implant or intravaginal ring users discontinued because of G.I.T. symptoms.

Other symptoms like headache, dizziness, weight gain, allergy, palpitation, weakness, anxiety, leg cramps, breast discomfort and pigmentation were more in cyclical pill users while multiple symptoms were commoner in once-a-month pill users as compared to other groups. One case taking Ovulen developed jaundice

TABLE I

Side Effects Responsible for Dropouts

Side Effects	Total No. of cases	Oral Pills			Injectables				Implants	I.V. Rangs
		Ovulen	Mini-pill	Pill-a-month	DMPA (61)		NET-OEN (68)			
					Mthly	Tri-mthly	Mthly	Tri-mthly		
	318	300	122	96	25	36*	34	34	70	20
—Mens. abnormalities	135	30** (10.0)	34 (27.9)	12 (12.5)	7 (28.0)	24 (66.7)	9 (26.5)	17 (50.0)	2 (2.9)	—
—G.I.T Symptoms	92	49 (16.3)	13 (10.7)	29 (30.2)	1 (4.0)	—	—	—	—	—
—Headache and dizziness	36	24 (8.0)	8 (6.6)	2 (2.1)	—	—	—	1 (2.9)	—	1 (5.0)
—Palp., Dysp., Anxiety, Weakness	14	4 (1.3)	4 (3.3)	5 (5.2)	—	—	1 (2.9)	—	—	—
—Wt. gain (4-10 kg)	13	9 (3.0)	3 (2.5)	—	—	—	—	1 (2.9)	—	—
—Allergy	10	8 (2.7)	—	2 (2.1)	—	—	—	—	—	—
—Pain in leg, back, chest	7	2 (0.6)	2 (1.6)	1 (1.0)	—	—	1 (2.9)	—	—	1 (5.0)
—Breast discomfort	5	3 (1.0)	—	2 (2.1)	—	—	—	—	—	—
—Jaundice & pigmentation	4	3 (1.0)	—	1 (1.0)	—	—	—	—	—	—
—Anaemia & hypertension	2	—	—	2 (2.1)	—	—	—	—	—	—

* Postpartum cases excluded, ** Figure in bracket shows percentages.

Abbrv.: Mens. abn.—Menstrual Abnormality, G.I.T. symp-Gastro-Intestinal Track symptoms, Palp.—Palpitation, Dysp.—Dyspnoea, Wt.—Weight.

and 2 women getting pill-a-month developed anaemia and hypertension. Intravaginal rings had to be removed during the study period in 2 cases because of side effects (lower abdominal pain and increased vaginal discharge in the 2nd cycle in one case, and severe headache, weakness, giddiness and tingling in left hand in the 5th cycle in the second).

Reasons for discontinuation

Side effects were responsible for discontinuation in 318 out of 737 cases followed (43.2%). One hundred fifty-two women (20.6%) had to discontinue because the drug was no longer available. If these cases are excluded the discontinuation rate for side effects becomes as high as 54.4%. Only 67 cases (9.1%) discontinued on valid grounds such as sterilization, desire for pregnancy, death or separation from husband. Twenty-three women (3.1%) discontinued as they conceived during drug therapy. The remaining 24% did not have any valid reasons for discontinuation.

Acceptability

Initial acceptability was high for all formulations and no difficulty was encountered in enrolling cases for the trial but continuation rates were poor as can be seen from Table III. At the end of 24 months the continuation rate for oral pills was only 1.9%, while the rates for monthly injections and subdermal implants were 4.0% and 12.8% respectively. The vaginal ring study was only for a period of 6 months and at that time 65% were still satisfied users.

Pregnancy Rates

A total of 23 pregnancies occurred in the course of the study. Of these 11 were in oral contraceptive users (4 with cyclical pills, 2 with mini-pills, 5 with pill-a-month), 11 occurred in implant users and 1 in a vaginal ring user. Table IV shows the period of use when pregnancy occurred.

Endometrial biopsies

Endometrial biopsies were done in 67 cases (42 getting injectables, 14 taking minipills, 6 using intravaginal rings and 5 with implants). Complete atrophy of the endometrium was seen in 36 out of 42 cases in the injectable group and uterine size was also found to be considerably reduced. No tissue was obtained in 50 out of 67 cases and hence no histopathological reports were available. In the remaining 17 cases the endometrium was non-secretory in 15 and secretory in 2 (one taking minipills and one getting 20 mg. Net-Oen injection monthly). Unilateral ovarian enlargement was found in 3 cases, 2 getting three monthly Net-Oen injections and 1 using intravaginal ring. Another ring user developed endocervical polyp (in second cycle) which on removal was reported as adenomatous polyp with chronic cervicitis. All these cases on subsequent followup 3-6 months after discontinuation of hormone therapy were found to be normal.

Comments

The following conclusions can be drawn from the study:

1. Oral contraceptive pills cyclically administered are a simple and very effective method of contraception provided the pills are taken regularly but our study high-lights the difficulty in getting women to continue taking these pills regularly

TABLE II

Reasons for Discontinuation of the Method

Hormonal contraceptives	Side Effects		Other reasons		Drug out of stock		Valid reasons		Pregnancy	
	No.	%	No.	%	No.	%	No.	%	No.	%
I—ORAL PILLS										
(A) Ovulen (300)	132	44.0	83	27.7	56	18.7	25	8.3	4	1.3
(B) Mini Pills (122)	64	52.5	40	32.8	15	12.3	1	0.8	2	1.6
(C) Pill-a-month (96)	56	58.3	26	27.1	2	2.1	7	7.3	5	5.2
II-INJECTABLES										
(A) DMPA										
(i) Monthly (25)	8	32.0	8	32.0	8	32.0	1	4.0	—	—
(ii) Tri-mthly. (36)	24	66.7	1	2.8	10	27.7	1	2.8	—	—
(B) NET-OEN.										
(i) Monthly (34)	11	32.4	10	29.4	6	17.6	7	20.6	—	—
(ii) Tri-mthly. (34)	19	55.9	7	20.6	7	20.6	1	2.9	—	—
III-IMPLANTS (70)	2	2.9	2	2.9	35	50.0	20	28.5	11	15.7
IV—I-.V. RINGS (20)	2	10.0	—	—	13	65.0	4 (Expulsion)	20.0	1	5.0
TOTAL: 737	318	43.2	177	23.0	152	20.6	67	9.1	3.1	

Other reasons—transferred, lost to follow-up unable to come, family objection.

Valid reasons—sterilization, desire for pregnancy, death or separation from husband.

TABLE III

Continuation Rate in Hormonal Contraceptive Users

Type of steroid contraceptives	Active Users							
	6 Months		12 Months		18 Months		24 Months	
	No.	%	No.	%	No.	%	No.	%
I—Oral Pills								
(a) Ovulen (360)	123	34.2	48	13.3	20	5.6	7	1.9
(b) Mini Pills (192)	39	20.3	30	15.6	19	9.9	Nil*	—
(c) Pill-a-month (100)	42	42.0	20	20.0	4	4.0	2	2.0
II—Injectables								
(a) DMPA								
(i) Monthly (25)	8	32.0	2	8.0	1	4.0	1	4.0
(ii) Three Monthly (36)	19	52.8	2	5.6	Nil*	—	—	—
(b) NET-OEN								
(i) Monthly (34)	18	52.9	8	23.5	1	2.9	Nil*	—
(ii) Three Monthly (34)	19	55.9	13	38.2	9	26.5	2	5.9
III—Silastic implants (70)	65	92.8	57	81.4	10**	14.3	9	12.8
IV—Intravaginal Rings (20)	13	65.0***	—	—	—	—	—	—

* Trial discontinued as drug was not available. ** Second implant was inserted in 10 women. *** Trial terminated after 6 months.

over long periods of time (only 5.6% of the women in this study continued with this form of contraception at the end of 18 months). Another drawback is that these pills cannot be given to lactating women during the first 6-9 months of lactation. Minipills, which do not have this handicap, and which are to be taken daily without any counting, were slightly more popular with 9.9% women continuing for 18 months when the study was terminated. Though drug intake is further simplified with the 'pill-a-months', these women complained of such intense nausea and vomiting that they did not want to continue with the method. Another drawback was the high pregnancy rate (5 out of 96 cases) due probably to the narrow margin of safety in terms of hypothalamic pituitary suppression which may result in rebound ovulation if the pill is taken just 2 or 3 days later than when it was due (Nudenberg *et al* 1973).

2. Injection of long acting progestational steroids proved to be a highly effective method of contraception which obviated the need of daily pill taking, but

TABLE IV
Occurrence of Pregnancy and Outcome

Month when pregnancy occurred	Ovulen* (2486)	Minipill (579)	Pill-a-month (685)	Implants (1023)	I.V. rings (96)
1	2 (MTPs)	1 (abortion)	—	2 (MTP—1 LSCS—1)	—
2	—	—	1 (MTP)	—	—
3	1 (FTND)	1 (FTND)	2 (MTPs)	—	—
4	—	—	—	—	—
5	—	—	—	—	1 (MTP)
6	—	—	1 (FTND)	1 (FTND)	—
7	—	—	1 (FTND)	—	—
8	—	—	—	—	—
9	1 (FTND)	—	—	1 (M.R.)	—
10	—	—	—	1 (M.T.P.)	—
11	—	—	—	1 (FTND)	—
12	—	—	—	4 (FTND—1, MTP—2, LSCS—1)	—
19	—	—	—	1 (MTP)	—
TOTAL	4	2	5	11	1
Pregnancy Rate	1.9**	4.2	8.8	12.9	12.5

* Women months. ** Per 100 woman years of exposure.

the high incidence of menstrual abnormalities which follow in the wake of the injections resulted in an 80% dropout at the end of 12 months showing that the method, though initially acceptable, is not so on follow up inspite of its efiectiveness. It may be pointed out that no adverse efiect on lactation was seen in 10 postpartum cases given these injections and none of the women getting DMPA injections developed breast nodules.

3. Silastic subdermal implants of long acting steroids constitute another promising method of contraception which obviates the need of both regular pill taying and repeated injections. Acceptability of the method was high with 81.4% continuing at the end of 12 months inspite of the

high pregnancy rate encountered with this method (11 pregnancies in 70 cases). The drawback of the method is that the implants have to be removed once they have lost their potency and most of the women objected to the minor operative procedure involved.

4. Our experience with intravaginal rings is far too small to make any comments on their general acceptability. The great advantage of this method is the fact that the rings can be inserted and removed by the users themselves after only elementray instruction from auxilary health or social workers. In this series of only 20 cases, 4 expulsions and 1 pregnancy occured during the six month period of follow-up. It appears that the method though simple may not prove very effective in view of the squatting position which is adopted for toilet purposes by rural women.

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