RANDOMIZED CLINICAL TRIAL WITH TRIQULAR - ED & LOW DOSE COMBINATION PILL

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ABSTRACT

A triphasic combined oral contraceptive pill Triquilar ED containing graded dose of Ethynyl oestradiol and levonorgestrel (group I) was compared with a fixed low dose combination pill (group II) in a multicentre clinical trial where a total of 383 women and 338 women were observed for 3098 and 2752 women months of contraceptive use respectively. Contraceptive reliability, bleeding pattern, side effects and metabolic parameters were compared among the users of the 2 types of oral pills. No pregnancies were observed in either of the groups during one year of pill use. The continuation rates were 71.0 and 74.2 per 100 women with Triquilar and Fixed Low Dose combination pills respectively at 12 months. The discontinuation rates due to side effects like menstrual problems and medical reasons were comparable in both the groups.

INTRODUCTION

Since oral contraceptive first became available in 1960's, over 60 million women worldwide have used them. The observation that side effects like cardiovascular diseases and venous thrombosis (Kay 1980) could be due to high dose of estrogen component of oral contraceptives led to reduction of the dose (of oestrogen) over time (Zador 1977). During last few years it has been reported that progestogens may also have an effect on blood pressure and changes in lipid profile (Larsson et al Cullberg et al 1979). This observation was responsible for development of the "Triphasic pills". These triphasic pills which mimic the hormonal release of a normal menstrual cycle contain progestogen and oestrogen in a varied ratio i.e. an oestrogenic predominance during the first part of cycle; higher and balanced level of oestrogen to progesterone during midcycle and a progesterone predominance during the later part of cycle in a manner resembling the normal hormonal pattern of the menstrual cycle. By varying the dose of oestrogen

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and progestogen the total steroid dosage has been reduced as compared to most of the fixed dose combination pills thus reducing the metabolic and physical side effects (Jeffery and Elis 1987).

METHODOLOGY

A multicentric randomized clinical trial comparing triphasic pill Triquilar ED - containing levonorgestrel and Ethynyl Oestradiol in graded doses (group I) with fixed low dose combination pill containing levonorgestrel & Ethynyl Oestradiol (group II) was carried out in eleven Human Reproduction Research Centres of the Indian Council of Medical Research.

The subjects included were healthy, informed female volunteers in reproductive age, exposed to risk of pregnancy and with no contraindications to use of oral contraceptives. The subjects were randomly allocated to either of the treatment groups.

A complete medical and gynaecological examination was done prior to the enrolment of the subject to rule out any contraindication. Follow up visits were scheduled at monthly intervals initially for 3 months and then 3 monthly for a period of one year to record regularity of pill intake, blood pressure, weight, menstrual pattern and other clinical events.

Both triquilar-ED and low dose combination pills were availble in a packet of 28 pills. The last seven pills in the pill packet were placebo. This treatment schedule of 28 days was repeated for a period of one year. The first treatment cycle was started from the first day of menstrual bleeding in subjects enrolled in either of the group.

Net cumulative rates were computed using the log rank technique and the test of significance was based on chi-square with one degree of freedom (Azen et al 1977). The menstrual pattern was analysed using the approach recommended by Rodriguez et al (1976).

OBSERVATIONS

Demographic Characteristics

A total of 721 subjects, 383 subjects with group I and 338 with group II were enrolled in the study. The subjects in group I and group II were observed for 3098 and 2752 woman months of use respectively. Both the groups were comparable with respect to age, parity, weight and height of the acceptors (Table I).

TABLE I

Demographic Profile

	Group I Mean ± S.D.	Group II Mean ± S.D.
No. of Acceptors	383	338
Age (yrs)	25.4±4.0	25.8±4.2
Parity	2.5±1.3	2.6±1.3
Height (cm)	150.7±5.9	151.3±5.8
Weight (kg)	45.1±6.9	45.2±7.0

Continuation Rates

The overall continuation rates at the end of 12

months were 71.0 and 74.2 per 100 users for Group I and Group II respectively. This difference was not statistically significant ($p > 0.05$).

Discontinuations

Women opted to discontinue the method due to various reasons ranging from medical side effects to personal reasons. There were no method failures in either of the 2 groups during the study period.

(i) Menstrual distrubances

Menstrual distrubances include alterations like heavy and prolonged bleeding, irregular bleeding and amenorrhoea. Discontinuations due to menstrual distrubances constituted 2.4 per 100 users in group I and 2.1 per 100 users in group II at 6 months of contraceptive use (Table II). At 12 months of pill use, the discontinuation rate increased to 4.0 per 100 users in group I and 2.6 per 100 users in group II. However the difference was not statistically significant.

(ii) Medical Reasons

Twenty-one subjects in group I and nine subjects in group II discontinued the method due to medical reasons giving the discontinuation rate of 6.9 per 100 users in group I and 3.4 per 100 users in group II at 12 months of drug use (Table II) ($p > 0.05$). Nine subjects discontinued the method due to giddiness, 2 subjects each due to Weight gain, Amoebiasis, Vertigo and one subject each for pain in abdomen, cervical dysplasia, chicken pox, jaundice, pain in joints and

TABLE II

Cumulative Discontinuation Rates per 100 users by reasons for discontinuation

Reasons	Rate + S.E.			
	6 months		12 months	
	Group I	GroupII	Group I	Group II
Method Failure	-	-	-	-
Menstrual Distrubances	2.4 ± 0.9	2.1 ± 0.9	4.0 + 1.2	2.6 + 1.0
Medical Reasons	5.2 + 1.2	2.9 + 1.0	6.9 + 1.4	3.4 + 1.1
Irregular Use of Method	2.6 + 0.9	4.4 + 1.3	3.1 + 1.0	5.4 + 1.4
Personal Reasons	9.6 + 1.6	11.9 + 1.9	16.2 + 2.1	16.6 + 2.3
Lost of Followup	4.4 + 1.1	4.8 + 1.3	5.2 + 1.3	5.3 + 1.3
Total Discontinuation Rate	20.1 + 2.2	20.4 + 2.3	29.0 + 2.5	25.8 + 2.5
Continuation Rate	79.9	79.6	71.0	74.2
No. of Acceptors at the begining of interval	383	338	255(127)	218(135)
Woman Months of use	1859	1610	3098	2752

(The no. in brackets indicate no. of subjects completing 12 months of method use).

allergic rash in group I, while four subjects discontinued due to giddiness, 2 subjects due to weight gain and one subject each for tuberculosis, jaundice and pain in joints in group II.

(iii) Irregular use of Method

The subject was discontinued from the trial for 'irregular use of method' in case 6 or more active pills were missed in one cycle. The discontinuation rates due to this reason were 3.1 and 5.4 per 100 users at 12 months for group I & II respectively (Table II) ($p > 0.05$).

(iv) Personal Reasons

The discontinuation rates due to personal reasons were 16.2 per 100 users in group I and 16.6 per 100 users in group II at 12 months of method use. Personal reasons include planning pregnancy, opted for sterilization etc. Discontinuation rates due to 'lost to follow up' at 12 months were 5.2 and 5.3 per 100 users for both group I & group II respectively (Table II).

Change in Body weight, Haemoglobin level and blood pressure

No significant changes in body weight was seen during the treatment in either of the groups. Haemoglobin status was monitored in all the acceptors at 6 monthly interval. There was no appreciable change in haemoglobin levels in either of the groups. The blood pressure of the subjects was monitored at each follow up visit

TABLE III

Clinical Chemistry Parametres (Mean + S.D.)

Group I	Centre I		Centre II		Centre III	
	0 Months	12 Months	0 Months	12 Months	0 Months	12 Months
Glucose						
0 hr.	91.5±7.5	92.9±8.0	91.6±6.8	92.3±6.0	68.3±14.0	70.8±10.5
2 hr.	88.8±9.2	93.2±8.5**	98.4±5.4	98.1±4.8	81.4±15.8	87.4±16.2
Total Proteins	6.6±0.6	6.8±0.5**	6.5±0.1	6.5±0.2	6.8±0.6	6.9±0.3
Albumin	3.8±0.6	4.1±0.5*	3.6±0.2	3.6±0.2	4.2±0.6	4.3±0.3
Cholesterol	165.0±25.5	175.4±35.0	188.1±12.9	189.8±9.2	167.8±14.6	188.9±32.5
HDL	39.9±3.7	39.6±15.4	Not done	Not done	Not done	Not done
Triglycrides	88.1±26.2	100.8±29.4*	88.5±15.2*	89.6±15.7*	107.4±20.8	129.8±44.2
SGOT	12.8±5.9	10.9±3.8	29.6±11.0	29.0±7.7	10.0±3.3	10.4±2.6
Bilirubin	0.4±0.2	0.4±0.2	0.5±0.1	0.5±0.1	0.4±0.1	0.4±0.2
Haemoglobin	10.7±0.7	11.2±0.6**	9.5±0.6	9.4±0.6	12.6±1.4	13.5±1.6*
Haematorit	37.4±4.1	39.0±4.0**	43.0±1.3	43.1±1.3	40.3±3.9	41.6±3.6
N	21		27		20	

* $P < 0.05$

** $P < 0.01$

Group II	Centre I		Centre II		Centre III	
	0 Months	12 Months	0 Months	12 Months	0 Months	12 Months
Glucose						
0 hr.	87.4±6.8	89.3±5.0	94.8±6.1	95.7±4.9	66.8±16.0	68.3±13.2
2 hr.	93.4±7.8	94.9±8.0	98.4±2.8	99.3±2.4	80.9±17.9	87.3±19.7
Total Proteins	6.7±0.6	6.8±0.4	6.5±0.2	6.5±0.2	6.7±0.9	6.8±0.4
Albumin	3.9±0.9	3.9±0.3	3.6±0.2	3.6±0.2	4.0±0.7	4.3±0.4
Cholesterol	168.0±29.0	178.6±32.9**	187.3±7.2	188.3±6.8	181.9±30.3	179.6±36.4
HDL	36.8±13.3	43.1±11.8*	Not done	Not done	Not done	Not done
Triglycrides	82.3±18.8	89.7±14.7**	85.0±9.3	84.8±10.1	113.3±35.0	112.5±42.2
SGOT	15.9±5.9	13.4±3.7*	28.5±3.6	28.7±3.5	13.0±5.3	14.7±5.0
Bilirubin	0.5±0.1	0.5±0.1	0.5±0.1	0.5±0.1	0.5±0.2	0.4±0.2
Haemoglobin	10.6±0.7	11.2±0.7**	9.3±0.7	9.4±0.4	13.2±1.8	14.4±2.1**
Haematocrit	37.3±3.4	38.9±2.5**	43.2±1.3	43.3±1.2	41.6±5.7	44.6±5.8*
N	23		20		13	

* P < 0.05

** P < 0.01

which remained within the normal range of 130/90 mm Hg in both the groups.

Menstrual Pattern

The menstrual pattern was analysed utilising the approach recommended by Rodriguez et al. The variables considered for evaluating the menstrual pattern in four reference periods were an average episode length, total no. of bleeding days and total no. of spotting days.

An average episode length of 22-35 days duration was considered as normal; 86.1 per cent and 84.3 per cent of subjects had normal average episode length in both the groups respectively during the first reference period, which was almost same till the fourth reference period.

Six to twenty bleeding days in a reference period of 90 days could be considered as normal. About 90 per cent of cases fall in this category throughout the study period. Further 42 per cent of the subjects in both the groups did not have any spotting during Ist reference period which decreased to 39.0 and 34.1 till 4th reference period in group I & II respectively.

Haematological and clinical chemistry parametres : Haematological parameters, (Hb, PCV) metabolic parameters, (glucose, cholesterol, HDL Triglycerides) Hepatic function tests, (Bilirubin, SGOT, total proteins, serum albumin, were determined before and after 52 wks of starting either of the oral pills at 3 centres. The data indicates that though there is a trend towards increase in post treatment values of some of the parameters, however the values remained with in the normal acceptable range (Table III).

DISCUSSION

The triphasic pills contain markedly lower total cycle doses of progestins, as compared to fixed dose combination pills. These triphasic pills are well tolerated, safe and effective as has

been reported in multicentre clinical trials carried out in United States, Canada and France (Pasquale 1984 & Culberg et al, 1982) in a randomized study compared levonorgestrel containing triphasic preparation (Triquilar) with a monophasic preparation. There were three pregnancies among 193 triphasic pill users. Two of the three pregnancies were considered drug failures and the third a possible drug interaction. There was no pregnancy in the monophasic group. Recently a report was published (Fay, R.A. 1982) with identical biphasic preparation citing 8 pregnancies during the year. However, in the present study no method failure was reported in the subjects using either Triquilar ED or fixed low dose combination pill during one year of contraceptive use.

The studies carried out with multiphasic formulation containing Norethinderone / levonorgestrel in combination with oestrogen in graded doses showed that bleeding patterns with triphasic pill were comparable with fixed low dose combination pill. (Pasquale 1984, Culberg 1982). A study, carried out in United States concluded that triphasics have little effect on breakthrough bleeding but observed that they may reduce the incidence of amenorrhoea, (Reiter 1990). In the present series the difference in bleeding pattern was not statistically significant in both the groups.

In the present series, though there is a trend towards increase in the post treatment values of some of the metabolic parameters however the values remained within the normal acceptable range. Similar observations were made in a study carried out by Notelovitz et al that in triphasic users even though HDL/LDL changes occured, the end point lipid values remained well within the clinically acceptable range.

The performance of Triquilar ED a triphasic pill was comparable to fixed low dose combination pills with respect to efficacy, continuation rates, menstrual cycle control and side effects. At present there does not appear to be a clear cut rationale for encouraging the use of triphasic pills in the National Welfare Programme. Further triphasic pills are generally more expensive than monophasics and may be difficult for many women to take them properly.

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