

AN OPTIMAL CONTRACEPTIVE PILL

(A Clinical Study)

by

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Despite high efficacy of oral contraceptives, the acceptance rate is low because of side effects. In this study an attempt has been made to select the low dose steroid formulations, depending upon the endocrine profile of an individual.

Majority of the side effects are related to estrogen/progestogen imbalance of the product. The content of estrogen and progestogen of various oral contraceptive pills varies and thus affect women's own hormonal balance. Whether a woman is predominantly estrogenic or progestogenic can be assessed from her menstrual symptoms and gynaecological examination.

In this study an attempt has been made to select a low dose steroid formulation depending upon endocrine profile of an individual and to assess whether the acceptability is thus increased and the number of drop-outs related to drug side effects is reduced.

Material and Methods

A total of 155 women were studied during a period of one year from Janu-

ary, 1971 to December, 1971. These cases were selected from the Family Planning Clinic of the Nehru Hospital attached to the Postgraduate Institute of Medical Education and Research, Chandigarh. Most of the subjects included in the study were taken up about 6 weeks postpartum.

At the initial visit after a thorough physical and gynaecological examinations, cases with varicose veins, hypertension, diabetes, heart disease and malignancy were excluded from the study.

Three different low dose formulations viz., Primovlar (Ethinyl estradiol 0.05 mg + Norgestrel 0.5 mg), Minovlar (Ethinyl-estradiol 0.05 mg + Norethisterone acetate 1.0 mg) and Norgestrel (0.05 mg each tablet) were employed.

Criteria for selection of a particular low dose steroid formulation was based on a tentative score of endocrine profile of an individual as shown in Table I.

Assessment

1. In each column of E and P the numbers were added. If total of E was the same or upto 5 greater than P, patients were given a balanced formulation (Primovlar).

2. If total of E was upto 6 or more greater than P, Progestogenic formulation was prescribed (Norgestrel 0.05 mg).

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TABLE I
Showing the Scoring According to Endocrine Profile

	Estrogenic E	Progestogenic P
A. Normal Menstrual Cycle		
Menstrual cycle irregular (varying more than 3 days in length)	2	-
Menstrual flow less than 4 days or scanty flow	-	3
Menstrual flow for 4-6 days or moderate flow	2	-
Menstrual flow over 6 days or profuse flow	3	-
B. Normal Cyclic Symptoms		
Premenstrual acne	-	2
Premenstrual tension	2	-
Premenstrual depression	-	1
Premenstrual oedema and swollen ankles	1	-
Premenstrual breast discomfort	-	1
Menstrual cramps	-	1
C. Previous Pregnancy History		
Nausea and vomiting	1	-
Dizziness	1	-
Hyperemesis	2	-
Chloasma	-	1
Excessive weight gain	-	1
D. General Physical Examination		
Dry vagina or thick white scanty discharge	-	2
Copious mucoid discharge; non-infective	1	-
Hormonal cervical erosion	2	-
Hirsutism	-	1

3. If total of E was less than P estrogenic formulation was prescribed (Minovlar).

Thus the patients were put on selected formulation as shown in Table II.

TABLE II
Showing Number of Cases Booked According to the Endocrine Profile

	No. of cases	Total No. of cycles
Primovlar	75	331
Minovlar	38	115
Norgestrel	43	148
Total	156	594

Results

Follow up was done every month for a minimum of 6 months and side effects were noted at each visit, through a semi-structured schedule.

Overall drop out rate in this series was 48.1%, drop out related to drug side effects being 12.8% only as shown in Table III.

It was also found that the difference in the drop outs in the different groups of formulation was not statistically significant ($P > 0.05$) as shown in Table IV.

The drop outs related to drug side effects were 75% of total drop outs and various causes in this category are shown in Table V.

TABLE III
Causes of Drop-out

Oral Contraceptive Used	Total subjects	Causes of Drop-out	
		Related to drug side effects	Not related to drug side effects
Primovlar	75	9	29
Minovlar	38	6	12
Norgestrel	43	5	14
Total	156	20 (12.8%)	55 (35.3%)

TABLE IV
Drop-out in Different Groups

Total No. of patients booked	Primovlar	Minovlar	Norgestrel	Total
	75	38	43	156
Drop-outs	38	18	19	75
Active patients	37	20	24	81

TABLE V
Causes of Drop-out Not Related to Drug Side Effects

	Primovlar	Minovlar	Norgestrel	Total
Apprehension and fear because of adverse propaganda	8	3	4	15
Husband's objection	4	2	2	8
Difficult to take 1 pill daily	5	3	3	11
Lost to follow up due to transfer from Chandigarh	5	2	2	9
Illness at home	3	—	1	4
Wanted to conceive in lactational amenorrhoea	1	1	1	3
Cause not known	2	1	1	4

Various side effects observed were as follows:

1. Nausea and vomiting

Incidence of nausea and vomiting in the 1st cycle was 8%, 10.4%, and 2.3% with Primovlar, Minovlar and Norgestrel respectively. This difference in the three groups is not statistically significant ($P > 0.05$). Incidence of nausea and vomiting in total cycles studied was 3.3%, 4.3%, and 2% respectively as shown in Fig. 1.

2. Headache and Dizziness

Headache mild and severe both were included in the side effects, but it was seen that headache was an occasional complaint. It was maximum in the first cycle and decreased altogether after the third cycle. First cycle incidence was 4%, 5.3%, 3.3% with Primovlar, Minovlar and Norgestrel respectively as shown in Fig. 2. Same patients had dizziness along with headache.

NAUSEA & VOMITING

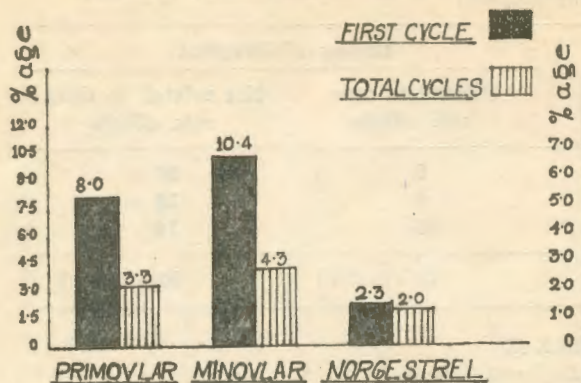


Fig. 1

HEADACHE

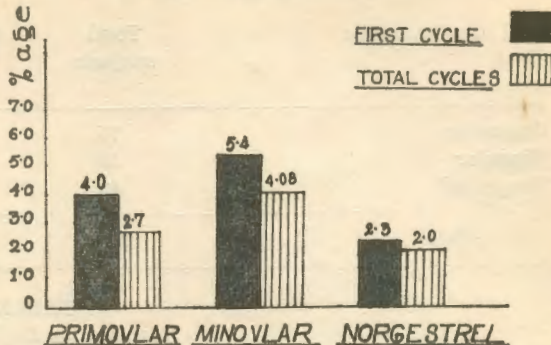


Fig. 2

3. *Spotting and Break-through Bleeding*

There was no relationship of break through bleeding according to the cycle of medication. Break through bleeding was rated when the patient had regular periods while taking the pills.

Incidence of the complaint in the 1st cycle was nil with Primovlar, 2.5% with Minovlar and 14.5% with Norgestrel and in the total cycles studied it was 0.3% with Primovlar, 0.8% with Minovlar and 10.3% with Norgestrel as shown in Fig. 3. Out of the Norgestrel series, 2 patients were changed to Minovlar after the second cycle due to the break through bleeding and this was followed by remission.

B.T.B. AND SPOTTING

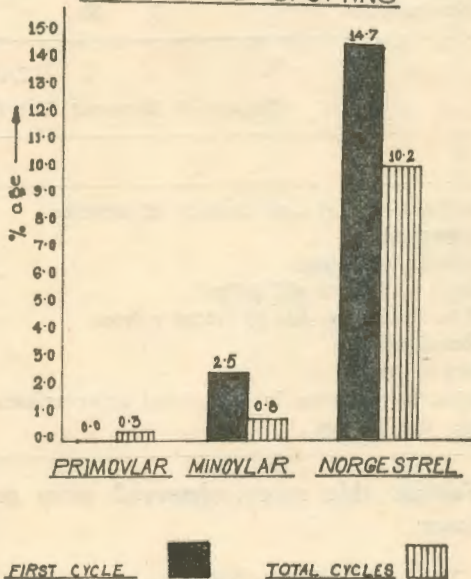


Fig. 3

4. *Amenorrhoea*

Criteria for amenorrhoea was when the patient failed to have withdrawal bleeding within seven days of the last pill. Amenorrhoea was not met with in the Minovlar cases, in the Primovlar group only 1 had amenorrhoea of 2 months but it was frequently seen in the Norgestrel group and their total cycles incidence was 4.1%.

5. *Menstrual Flow*

It remained moderate in 93.7%, 87.5% and 78.3% of cases of Primovlar, Minovlar and Norgestrel. Initial flow before medication was compared with the flow after six months of medication in active cases.

6. Change in Weight

Incidence of significant weight gain or weight loss of more than 10 lb., was not found in any case on the three different formulations. Of the total 15% gained weight between 1-5 lbs. and 0.6% between 5-10 lbs. Similarly, weight loss of 1-5 lbs. was noticed in 14.6% of cases, while 3.6% lost weight between 5-10 lbs. (Details are shown in Fig. 4).

EFFECT OF P. M. & N. ON WEIGHT

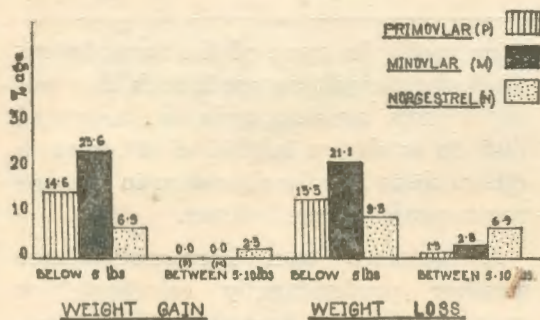


Fig. 4

7. Breast Discomfort

It was an insignificant complaint seen only in 0.6% cases on Primovlar and 0.3% in Norgestrel group.

8. Effect on Quantity of Lactation

In the present study, in 77% of cases there was neither increase nor decrease in lactation. In the remaining 23% of cases there was decrease in lactation after 3 to 4 months of medication as assessed by patients' own subjective feeling. The minimum decrease in the lactation was seen in the Norgestrel series, being 9.4% while with Primovlar and Minovlar it was 30% and 29% respectively as shown in Figure 5.

There was no increased incidence of pigmentation and psychological changes. One patient on Primovlar developed

swelling all over the body with marked itching, but there was a positive history of allergy in the past and so this was not attributed to the drug but the drug was discontinued.

Besides the side effects, certain beneficial effects were also noted such as correction of menstrual irregularities which occurred in all cases on combination pills, viz. Primovlar and Minovlar. There was complete remission of dysmenorrhoea in the Primovlar and Minovlar group, but among the Norgestrel group

DECREASE IN LACTATION

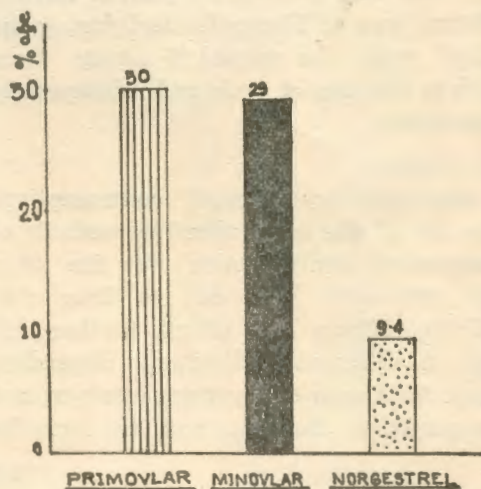


Fig. 5.

there was decrease in dysmenorrhoea only in 52% of cases and unchanged in 48% of cases, but there was no aggravation of this symptom in any case.

As shown in Table III 20 patients i.e. 12.8% dropped out due to drug side effects. The detailed analysis of the number of cases dropped out according to the side effects with results on the 3 different formulations are shown in Table VI.

TABLE VI
No. of Patients Drop-out Due to Drug Side Effects

Reasons for drop out	Primovlar	Minovlar	Norgestrel
Nausea and vomiting	2	2	1
Headache and dizziness	3	3	1
Spotting and B.T.B.	-	-	3
Scanty period	-	-	-
Breast discomfort	1	-	-
Change in weight	-	-	-
Change in lactation	2	1	-
Allergic reaction	1	-	-
Depression	-	-	-
Total	9	6	5

Drug Efficacy

Drug efficacy in the present series was 100% but one pregnancy was reported and this was because of patient failure. Patient was on Primovlar and during the third cycle she missed 6 tablets from 14th to 20th day of cycle and subsequently conceived.

Discussion

Although oral steroid contraceptives are one of the most effective methods of temporary contraception, yet the drop out rates are high due to drug side effects. These side effects further differ in different individuals depending upon their own endogenous estrogen and progesterone secretion and the formula-

tions used. In some of the formulations used, the steroid content is such that women's own ovarian cycle is suspended due to ovulation inhibition whereas in others there is only alteration in the estrogen progesterone balance.

A woman's own hormonal balance whether predominantly estrogenic or progestogenic can be assessed from menstrual cycle symptoms and gynaecological examination (3) based on these observations a clinical proforma was designed by a tentative scoring method for selection of particular formulation for a particular individual. The side effects with same formulation used at random are shown in tables VII and VIII.

TABLE VII
Comparison of Side Effects When Primovlar Was Prescribed at Random With the Present Series, Comparison of Side Effects in the Final Cycle Only

	Present series	Statzer	Satterthwaite
No. of patients studied	75	424	725
Total cycles studied	331	9676	1650
Nausea and vomiting	8.0%	24.5%	7.0%
Headache	4.0%	13.5%	9.1%
Dizziness	5.3%	17.3%	5.5%
Spotting and B.T.B.	-	2.9%	2.6%
Breast discomfort	0.3%	0.3%	-
Flow (average)	93.8	68.2	90.6
Flow	6.9%	13.0	4.2
Flow	-	18.8	5.8

TABLE VIII
Comparison of Side Effects in Total Cycles

	Present series	Statzer	Satterthwaite
Nausea and vomiting	3.3%	5.7%	1.6%
Headache	2.7%	11.6%	6.6%
Dizziness	2.3%	4.7%	2.5%
Spotting and B.T.B.	0.3	2.3	1.1
Breast discomfort	0.3	0.3	2.0
Wt. loss (5 lb. or over)	1.3	4.3	2.0
Wt. gain (")	-	2.8	2.6
Flow average	92.8	87.1	94.6
Less	7.2	5.3	3.8
More	-	4.4	1.6

These Tables indicate that proper selection of a pill reduced the incidence of the side effects but it could not be proved statistically because of marked variation in the number of cycles studied in the series and other two comparable series.

Estradiol 0.05 mg., 38 cases and Norgestrel (0.05 mg.) tablet, 43 cases. The proper pill was selected depending upon the endocrine profile of the individual patient which was based on her menstrual history, previous pregnancy state, menstrual symptoms and detailed physical and

TABLE IX

Comparison of Side Effects When Norgestrel Prescribed at Random is Compared With the Present Series (Duration of use of 6 months 1 year in both series)

	Present series	Mears et al
No. of patients studied	43	43
Total cycles studied	148	433
Headache	2.1	13.0
Dizziness	2.0	9.0
Spotting and B.T.B.	2.1	212.0
Breast discomfort	-	16
Drop out related to drug side effects	11.6	38.0

The Tables show statistically significant difference between the two series ($p < 0.01$). There was no comparable study for the Minovlar group and thus its side effects could be compared.

Conclusions

One hundred and fifty-six patients were given three different formulations—Primovlar (Norgestrol 0.5 mg. + Ethinyl estradiol 0.05 mg) 75 cases; Minovlar (Norethisterone Acetate 1 mg. + Ethinyl

gynaecological examination by a tentative scoring method. The incidence of various side effects were nausea and vomiting 2-3%, headache—25.4%. Dizziness 2.1-4%; breast discomfort 0.3 to 0.6%. Weight did not vary more than 5 lb in 95.7% cases. These side effects were 2-3 times less than that reported by various workers by using the same formulations at random. The menstrual flow remained moderate in 78-93.8% cases. The breakthrough bleeding and

amenorrhoea was negligible in combination pill and was 10.2% with Norgestrel which was 2-4 times less as compared with the same formulation used at random.

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