

TREATMENT OF UNEXPLAINED INFERTILITY WITH CLOMIPHENE CITRATE (FERTYL)

by

R. RAJAN,* M.D., D.G.O.

and

K. AMBIKA DEVI,** B.Sc., M.B.,B.S.

Because of the safety and convenience of administration, clomiphene citrate, in addition to its role as a powerful ovulation inducer, is also employed for a wide variety of conditions in infertility practice. By far the most widely accepted indication for clomiphene use is induction of ovulation in the infertile, anovulatory women (Greenblatt *et al* 1961; Roy *et al* 1963; Kistner, 1966; and Kase *et al* 1967). Subsequently, clomiphene has also been suggested as therapy for luteal phase defects in selected patients (Echt *et al* 1969; Jones, 1976; Garcia *et al* 1977; and Andrews, 1979). Recent report by Quagliarello and Weizz (1979) favours the use of clomiphene in infertility associated with shortened luteal phase. Clomiphene therapy is also indicated for oligo-ovulators who are unable to establish a pregnancy because of the infrequent ovulation (Huppert, 1979). In addition, clomiphene has a diagnostic role in evaluating the integrity of the hypothalamic-pituitary axis and investigating menstrual disorders (Wentz *et al* 1976 and Jones *et al* 1977).

While administration of clomiphene to normally ovulating women is not recommended, it is appropriate to use clomiphene to regulate ovulation in women who are candidates for donor artificial insemination (Klay, 1976; Beck and Barrett, 1978, Rajan, *et al* 1980). Because of the emotional stress of the procedure the cycles may become erratic and unpredictable, and the use of clomiphene permits predictable timing of ovulation and a more effective scheduling of inseminations. Similarly clomiphene has been employed as adjunctive therapy following surgery for endometriosis in infertile women (Buttram, 1979).

We administered clomiphene citrate (Fertyl) in a group of childless women with 'unexplained infertility' with a view to evaluate the fertility rate as compared to the spontaneous conception rate possible in a similar group. Since a considerable number of women with unexplained infertility conceive following the preliminary infertility work-up and prior to any recognised form of therapy, a reasonable period of waiting, upto one year if below 30 years, or 3 to 6 months if elderly, is justifiable before scheduling any detailed investigative procedures or treatment modalities (Rajan and Ambika Devi, 1980). However, our present study is aimed at finding out whether the pregnancy rate can be further improved in this

*Associate Professor,
Department of Obstetrics and Gynaecology,

**Research Assistant,
Intertility Research Project,
Medical College Hospital, Alleppey-688 001,
Kerala.

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group of patients by treating them with clomiphene immediately after the preliminary infertility work-up.

Material and Methods

Over a period of 3 years, beginning from November 1976, the senior author has registered 793 infertile couple for evaluation and treatment. Among them 161 couples after the preliminary investigations, were found to have no explainable cause for infertility and they were managed by the following two schedules:

(i) Randomly selected 101 couples given reassurance and were advised to wait for a period of 3 months to 1 year for spontaneous conception to occur.

(ii) The remaining 60 couples were scheduled for clomiphene therapy in the female partner following the preliminary investigations, the duration of treatment limited to 3 consecutive cycles.

The various parameters, such as the age of the male and female partners, duration of infertility, and the investigative procedures adopted in both groups of patients were comparable (Table I).

Our criteria for unexplained infertility were as follows: An ovulatory menstrual cycle as judged by premenstrual endometrial biopsy and in some cases basal body temperature recordings, normal sperm count (20 million or more per ml

of semen) and good progressive motility (grade 2+ or more), a positive post-coital test, and normal findings at hysterosalpingography (HSG).

Schedule of administration of clomiphene (Fertyl): Treatment with clomiphene was started in the immediate next cycle following the investigative procedures. The dose was 50 mg administered daily for 5 days beginning on the 5th day of the cycle. Regular coitus, preferably on alternate days, was advised, especially after completion of the 5 days treatment. The total number of treatment cycles were limited to 3 consecutive months.

Results

Of the 60 patients in the clomiphene group, 23 conceived within 3 months of treatment, giving a pregnancy rate of 38.33 per cent. Another 6 patients (10 per cent) conceived in the immediate non-treatment cycles, amounting to a total conception rate of 48.33 per cent (29 patients). Age of the successfully treated patients ranged from 21 to 41 years with a mean of 25 years, and the duration of infertility ranged from 1 to 10 years with a mean of 3.44 years. These figures compared favourably with the age and duration of infertility given for the entire series in Table I. Further break

TABLE I

Details of the patients	Unexplained infertility clomiphene group	Unexplained infertility no-treatment group
No. of patients studied	60	101
No. conceived	23 (38.33%)	32 (31.68%)
Age of the male partner	24 to 50 yrs. (32.94)	23 to 55 yrs. (32.28)
Age of the female partner	19 to 41 yrs. (26.41)	19 to 42 yrs. (26.40)
Duration of Infertility	1 to 18 yrs. (4.66)	1 to 17 yrs. (3.92)
Age of the patients who conceived	21 to 41 yrs. (25.00)	19 to 37 yrs. (25.46)
Duration of Infertility of the pregnant women	1 to 10 yrs. (3.44)	1 to 10 yrs. (3.12)

Mean values are given in the bracket.

down of the age factor showed that the pregnancy rate was just more than 40 per cent in women who were below 30 years, with the pregnancy rate falling to 20 per cent in the age group of above 30 years (Table II). Similarly, the pregnancy rate was nearly 45 per cent for those with a duration of infertility ranging upto 5 years, beyond which the pregnancy rate was only 25 per cent (Table III).

By contrast, in the 'no-treatment' group (placebo group) only, 32 of the 101 subjects conceived, that too within a period of 1 year, giving a pregnancy rate of 31.68 per cent. Age of the patients who achieved conception ranged from 19 to 37 years with a mean of 25.46 years, and their duration of infertility ranged from 1 to 10 years with a mean of 3.12 years. These figures too did not differ much from that of the entire series (Table I). Influence of age of the patient and the duration of infertility on the pregnancy rate is given in Tables II and III respectively.

Among the 23 conceptions occurring in the clomiphene treated group, 13 (56.50

per cent) were recorded by the first cycle of clomiphene administration (Table IV), and all had conceived by 3 cycles of treatment. Nevertheless, in the placebo group, only 16 women (15.84%) conceived within the first three months following the infertility work-up, and the remaining 16 women conceived over a period of 4 to 12 months (Table IV).

Discussion

Our studies indicate that the short-term administration of a low dose of clomiphene citrate increases fertility in women with so-called unexplained infertility. While the mechanism by which the fertility is improved is not clear, it may be possible that the ovulation regulation achieved by clomiphene therapy overcomes the influence of the emotional stress of these subjects. It is also possible that some of these patients have minor ovulatory disorders like infrequent ovulation which was not diagnosed by the routine investigative procedure, but promptly corrected by clomiphene treatment. It can also be that an occasional

TABLE II
Age and Fertility Rate

Age of the patients	Clomiphene group			No treatment group		
	Total patients	No. conceived	%	Total patients	No. conceived	%
Upto 25 years	29	12	41.37	50	15	30.00
26 to 30 years	21	9	42.85	30	13	43.33
Above 30 years	10	2	20.00	21	4	19.04

TABLE III
Duration of Infertility and Fertility Rate

Duration of Infertility	Clomiphene group			No-treatment group		
	Total patients	No. conceived	%	Total patients	No. conceived	%
Upto 5 years	44	19	44.18	81	30	35.71
Above 5 years	16	4	25.00	20	2	10.00

TABLE IV
Comparative Analysis of Pregnancy Rate

Unexplained infertility clomiphene group		Unexplained infertility No-treatment group	
Total pregnant (within 3 months)	23 (38.33%)	Total pregnant (within 12 months)	32 (31.68%)
Conception in the:		Conception in:	
1st clomiphene cycle	13 (56.50%)	3 months	16 (50.00%)
2nd clomiphene cycle	6 (26.10%)	6 months	7 (21.87%)
3rd clomiphene cycle	4 (17.40%)	12 months	9 (28.13%)
Conception in the subsequent 3 non-treatment cycles	6 (10.00%)		
Total conception in 6 months	29 (48.33%)	Total conception in 6 months	23 (22.77%)

luteal phase defect or a shortened luteal cycle is being corrected by this form of treatment resulting in conception.

In order to prove that clomiphene administration has a definite therapeutic role in women with unexplained infertility we have compared the results with that of spontaneous conception occurring following infertility work-up. It is noteworthy that the increased conception rate in the clomiphene group is achieved within a short period of three months. While 38 per cent of clomiphene users had conceived within 3 months of treatment, only 15 per cent of women had achieved spontaneous conception within 3 months following the basic investigations. It is a fact that about 32 per cent of women have spontaneous conception following infertility work-up, but 50 per cent of these conceptions were achieved by waiting for a period of 4 to 12 months. Contrarily, in the clomiphene group, over the 38 per cent conception rate, another 10 per cent conceived within another 3 non-treatment cycles, giving a total conception rate of 48 per cent over a period of about 6 months.

We have selected a low dose therapy with 50 mg of clomiphene administered for 5 days. This is a very safe dose schedule which is expected to produce

minimal or no complication even in women who are regularly ovulating. Hence there is no disadvantage in using this drug, but the advantage is that there is an increased conception rate and that too within a short period of treatment.

It is felt that 3 months treatment with clomiphene is too short a period for therapeutic trial. Since 75 per cent of the spontaneous conceptions result within 6 months of the preliminary investigations and many women are prepared to wait for 6 months, it may be only reasonable that clomiphene administration is tried for 6 cycles. By increasing the duration of therapy to 6 cycles, which in no way will affect the safety of the procedure, we feel that still further improvement in pregnancy rate could be realised.

Conclusion

In conclusion, it can be said that increased fertility rate, short period of therapy, safety and convenience of administration are the factors recommending the use of clomiphene for women with 'unexplained' infertility. We consider this as yet another indication for clomiphene therapy in infertility practice.

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