

# OVULATION REGULATION WITH CLOMIPHENE CITRATE (FERTYL) FOR THERAPEUTIC INSEMINATION

by

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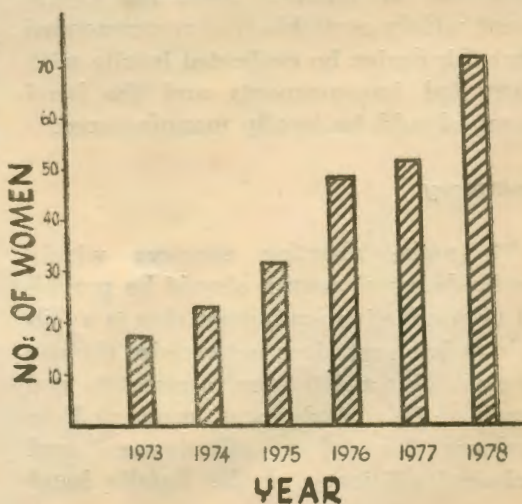
Evaluation of 1220 infertile couples over a period of 6 years, between 1973 and 1978, has clearly shown that male factor is solely or partly responsible for the barren union in 50 per cent of the couples. Seminal study of these infertile men discloses that every 3rd man with a male defect is azoospermic. Confirmatory bilateral testes biopsy performed in 210 consecutive azoospermic men has revealed irreversible tubular damage in 50 per cent such subjects (Rajan, 1978). From this analytical data it may be considered that every 6th infertile man is irreversibly sterile with no scope for any treatment.

After having elucidated the magnitude of the problem of male infertility we would prefer to focus the attention on providing an alternate solution for the couples presenting with intractable male factor. There are only two ways open for them: (i) therapeutic insemination with donor semen, and (ii) adoption. Better knowledge of human reproductive

biology, convincing proof for irreversible testicular dysfunction, and improved education which enables proper understanding of the problem have escalated the role of therapeutic insemination in infertility practice, and presently insemination is a better choice for many couple over adoption.

During the last 6 years, the senior author has performed AID in 240 women whose husbands were chronically defecient, and a break down of this figure (Fig. 1) shows a steep increase in the

FIG. I  
A.I.D IN 240 WOMEN OVER 6 YRS.



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\*Presented at first All Kerala Conference of  
Obstetrics & Gynaecology, Calicut, April 1979.

Accepted for publication on 11-4-1979.

number of couples requesting AID every year. With the increasing demand and with the aim of best results within a short period of treatment, we have continuously modified our method of screening the female, technic of placing the semen and timing of insemination (Table I).

period of 2.53 cycles (Rajan *et al.*, 1979).

To maximise the results, in a field where prompt success is the goal, presently we prefer to regulate ovulation with clomiphene citrate (Fertyl) for proper timing of insemination. Failure to con-

TABLE I  
Various Modifications of A.I.D. Schedule

Author(s)	Insemination Schedule	Pregnancy rate (%)	Mean Cycles of insemination
Rajan (1976)	Insemination without a prior evaluation of the female	37.50	6-8 cycles
Rajan (1978)	Insemination without prior female evaluation	51.60	5.25
Rajan, Joseph and Usha (1979)	Female fertility status evaluated: Ovulation determined by BBT, and endometrial biopsy. Tubal patency determined by air insufflation method	56.86	2.45
Rajan, Joseph and Usha (1979)	Female fertility evaluated: Ovulation, determined by BBT and endometrial biopsy Tubal and uterine factors evaluated by hysterosalpingogram (HSG)	66.60	2.53
Rajan and Rosamma John (1978)	Female fertility status not evaluated Regulation of ovulation with clomiphene citrate	70.00	1.30
Present series	Intensive evaluation of female: Ovulation determined by BBT Tubal and Uterine factors considered by HSG. Advanced prediction of ovulation by clomiphene-regulated ovulation	78.20	2.10

Prior to insemination tubal and uterine factors are evaluated in all women by a hysterosalpingogram (HSG), and ovulation is diagnosed and timed by looking for biphasic shift in the basal body temperature curve (BBT). Usually insemination is performed on two alternate days between 11th and 15th day of the cycle which quite often corresponds to the biphasic shift. Employing this insemination schedule we have recorded a success rate of 66.60 per cent with pregnancy resulting in a mean treatment

ceive following insemination in a properly screened woman treated with good quality fresh semen, we feel, is probably due to difficulty in determining ovulation and improper timing of insemination. If so, this problem can be circumvented by medical regulation of ovulation where ovulation can be predicted well in advance and insemination planned accordingly. Our experience with clomiphene-regulated ovulation in 55 women undergoing AID, forms the text of this presentation.

**Clomiphene-Regulated Ovulation**

As mentioned earlier, all the 55 women who had reported for AID were thoroughly evaluated for all the parameters for fertility. The age of these patients ranged from 22 to 39 years with a mean of 28 years, and their duration of infertility ranged upto 15 years. Ovulation was regulated with clomiphene citrate in the following manner:

Between the 5th and 7th day of the cycle therapy with clomiphene was started in a dose of 50 mgms (1 tablet) administered daily for 5 days. Regular BBT recording was maintained, and

ovulation was anticipated between 5th to 9th day following completion of clomiphene therapy (Figs. 2 and 3).

**Timing of Insemination**

The days of insemination were calculated well in advance at the time of initiation of clomiphene therapy. Insemination was done twice in a particular cycle on days 5th and 7th following completion of clomiphene therapy, and this period quite often coincided with the thermal shift in the BBT (Figs. 2 and 3). The method of insemination was the cervico-vaginal technic with the patient in the dorso-lithotomy position for about 10 minutes.

Gynaecologist:  
Dr. R. Rajan M. D., D. G. O.

Fig. II

**BASAL BODY TEMPERATURE CURVE  
TIMING OF OVULATION**

Registration No. T455  
Cycle No. 3 A 89

Name Smt. S. P.  
Age 26 yrs.  
Menses began on 19-6-'78 Taken at \_\_\_\_\_  
Duration of flow 4 days

Year 1978  
Month June - July  
Cycle length: \_\_\_\_\_ days

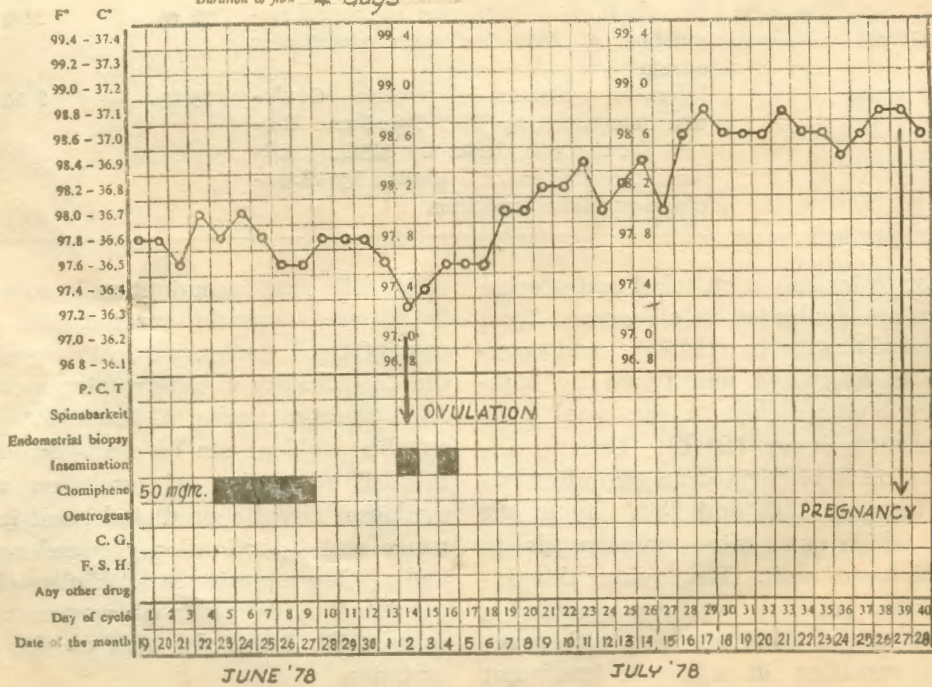


FIG. III

BASAL BODY TEMPERATURE CURVE  
TIMING OF OVULATION

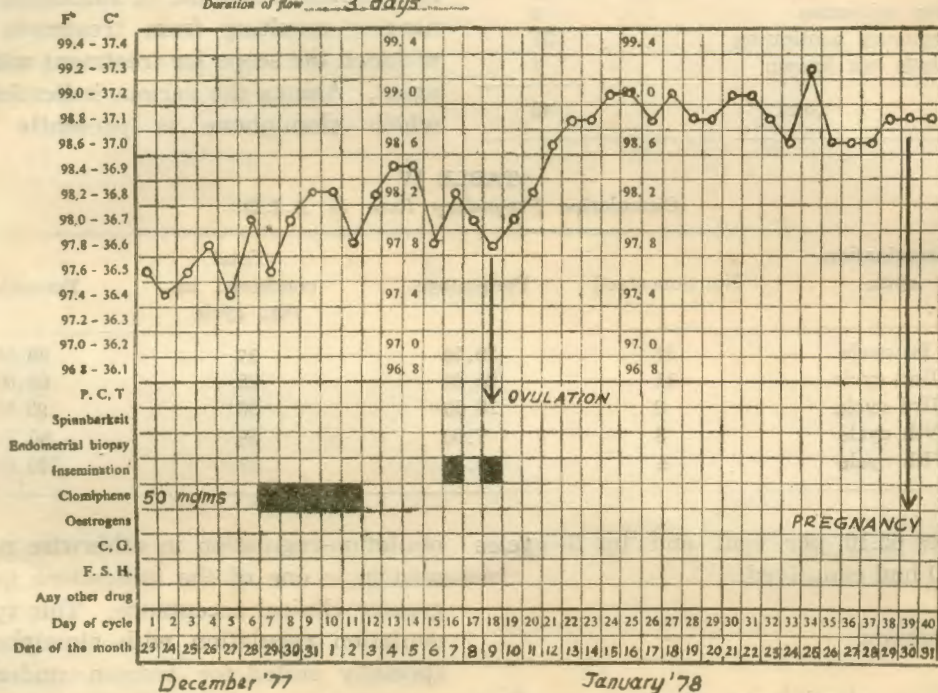
Registration No. T.152  
Cycle No. 1 A4

Gynaecologist

Dr. R. Rajan M. D., D. G. O.

Name Smt. B.A.  
Age 28 yrs.  
Menses began on 23-12-77  
Duration of flow 3 days

Year 1977-78  
Month Dec. Jan.  
Cycle length: \_\_\_\_\_ days



Fresh, good quality semen collected from students were employed for this purpose.

Usually 3 to 6 treatment cycles are tried in women who do not conceive within 1 or 2 cycles. Those who had 6 consecutive unsuccessful attempts were subjected to laparoscopic evaluation or for laparotomy for evidence of any undetected tubo-peritoneal cause of infertility.

TABLE II  
Results of Clomiphene-Regulated Ovulation for A.I.D.

Total women inseminated	55
Number conceived	43
Pregnancy rate	78.20%
No. of treatment cycles	1 to 6
Mean treatment cycles	2.10

Effect of Ovulation Regulation (Table II)

Among the 55 women who had clomiphene-regulated ovulation for AID, 43 conceived within 1 to 6 cycles of insemination. This gives a success rate of 78.20 per cent in a mean treatment period of 2.10 cycles. There were three abortions (7.00 per cent) and two twin deliveries (4.70 per cent) for the 43 conceptions. There were no antenatal or intranatal complications for these gravidae. The pregnancy outcome of these patients are given in Table III.

The cumulative pregnancy rate is presented in Table IV. Of the 43 women who conceived 17 women did so in the first cycle itself (39.50 per cent). By 2

TABLE III  
Pregnancy Outcome Liver 43 Women

Normal deliveries	6
Caesarean sections	5
Abortions	3
Twin deliveries	2
Pregnancy continuing	23
Details not known	4
<b>Total</b>	<b>43</b>

with no higher rate of birth defects than that for normally conceived infants (Merrell-National Lab., 1972).

Wider use of clomiphene, proved safety and increased number of successful pregnancies resulting from treatment have widened the scope for treatment with this agent. Among the various indications for which clomiphene is presently used,

TABLE IV  
Cumulative Pregnancy Rate in A.I.D.

Insemination cycle	No. conceived	Percentage	Total conceived in that cycle	Percentage
Ist cycle	17	39.50	17	39.50
IInd cycle	11	25.60	28	65.00
IIIrd cycle	8	18.60	36	83.70
IVth cycle	3	7.00	39	90.70
Vith cycle	4	9.30	43	100.00

cycles 65.10 per cent and by 3 cycles 83.70 had conceived.

#### Discussion

Since clomiphene citrate was first described for the use of ovulation induction by Kistner and Smith (1960) and Greenblatt (1961), it presently is the most successful single agent for treatment of anovulatory infertility (Kase, 1973; Rakoff, 1976; and Garcia *et al.*, 1977). It is generally agreed that women with normal hypothalamic-pituitary-ovarian axis but unable to ovulate respond well to clomiphene induction. The series of action initiated by clomiphene results in ovulation about 11 to 14 days after starting the medication, sometimes a few days earlier, rarely later. Over 10 years experience with clomiphene citrate (Garcia *et al.*, 1977) has clearly proved the safety of the product, and more than 2000 successful pregnancies have been reported,

ovulation-regulation in otherwise normal woman is one of the indications gaining greater clinical acceptance. This type of ovulation regulation with clomiphene is specially suited for women undergoing insemination where determination of ovulation is difficult due to the stress produced irregular or delayed ovulation (Murphy and Torrano, 1961).

In addition, clomiphene regulation allows for prediction of ovulation well in advance for proper timing of insemination. Moreover, clomiphene administration can be altered to start the therapy on any day between 4th to 7th days of the cycle, so that the insemination day will fall on days convenient to the couple and physician and more important that the donor is available. All these factors benefit the patient by maximising the pregnancy rate and allowing a decrease in the total number of treatment cycles required and thus reducing the emotional and financial stress on the patients.

Among the 55 women who had clomiphene-regulated ovulation for AID in our series, 78.20 per cent had become pregnant in an average of 2.10 treatment cycles, as compared with success rates reported by us earlier ranging from 37.50 per cent to 66.60 per cent (Table I). With all other parameters comparable, such as technic of insemination, use of fresh semen and female evaluation, we attribute the high success rate to reliable ovulation induction at a predictable time and proper timing of insemination.

A 50-mg, five-day course of clomiphene therapy was planned in all women and the treatment was initiated between the 5th to 7th day of a cycle. Thermal shift, indicating ovulation, was quite often recognised between 5th to 9th day following completion of clomiphene therapy. Hence insemination was performed on 5th and 7th days after the last tablet.

Of the 43 women who became pregnant 3 had aborted in the first trimester, and 2 had twin deliveries. Incidence of abortion which works to 7 per cent is not high compared to the pregnancies conceived by AID subjects not treated with clomiphene (Rajan, 1978). However, there is a definitely greater incidence of multiple pregnancy (4.70 per cent). There were no birth defects in any of the babies born or was their any intranatal complications in the pregnant mothers.

Reporting on artificial insemination, Klay (1977) has described the highest success rate of 86 per cent following clomiphene regulated ovulation. He has attributed the high success rate to, first, reliable ovulation induction at a predictable time, and second, using fresh semen, which has been shown to give better pregnancy rates than frozen semen. Moreover, he had used cervical cap into

which the semen was placed and was then attached directly to the cervix so that there was continuous contact with the cervix to allow for sperm migration. The cervical cap was left in place for 12 hours, and was then removed by the patient.

#### *Acknowledgement*

The authors are grateful to the medical superintendent of MCH, Kottayam, for the kind permission to use the hospital records related to the infertility evaluation.

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