

# SERIAL URINARY OESTROGEN AND PREGNANDIOL ASSAYS IN WOMEN ON CLOMIPHENE CITRATE

by

PRATIBHA R. VAIDYA,\* M.D., F.C.P.S.

(Miss) BHARATI A. DESHPANDE,\*\* M.Sc.

NERGESH D. MOTASHAW,\*\*\* M.D., F.R.C.S.

and

VITHAL N. PURANDARE,\*\*\*\* M.D., F.R.C.S.

## Introduction

Clomiphene Citrate is a widely used drug for induction of ovulation in suitable cases of anovulation with infertility. Although ovulation can be successfully induced in 70% of women, conception rate is only 25.40% of the ovulated patients. Proper monitoring of the induced cycle is very important. We thought of studying the Serial urinary oestrogens and pregnanediol excretion in women on induction of ovulation with this drug has been studied.

## Maternal and Methods

This is a prospective study of serial urinary oestrogen assay by Brown's (1955) Semiautomatic Spectrofluometric method and the pregnanediol assay by De' Watteville's (1948) method. In all 19 women on clomiphene citrate were studied for 34 cycles. Twenty-one cycles were ovulatory and 13 cycles were anovulatory. Among these 19 women, ovulation occurred in one or more more cycles in 10 women but other 9 remained anovulatory during the study period. Only those women willing to collect 24

hours urine at least twice a week were accepted for the study. Ovulation was also documented by parameters such as B.B.T. chart, serial vaginal cytology, cervical mucus study and endometrial biopsy. The drug was administered orally 50 mg/day for 5 days from 5th to 9th day of the cycle or withdrawal bleeding in the first cycle. If ovulation failed to occur in this cycle the dose was stepped up to 100 mg/day for 5 days in next two cycles.

## Results

Graph I indicates the first oestrogen peak in 21 ovulatory cycles. The minimum level of oestrogen peak was 30  $\mu$ g/

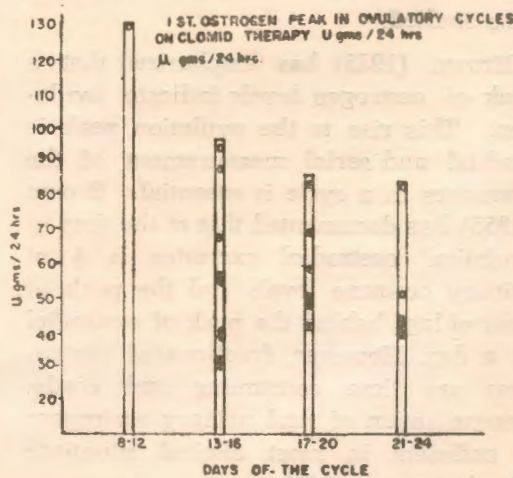


Fig. 1

From: Department of Obstetrics and Gynaecology, K.E.M. Hospital, Parel, Bombay-400 012.

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24 hours and the maximum level was 130  $\mu\text{g}/24$  hours and in 17 cycles the peak was ranging from 40  $\mu\text{g}$  to 85  $\mu\text{g}/24$  hours. In 15 cycles this 1st peak of oestrogen occurred from 13th to 20th day of the cycle. In only one cycle the oestrogen peak occurred on 10th day and in other 5 cycles the first oestrogen peak was late and occurred around 21st to 24th day. This proves that in most of the women ovulation occurs around 4 to 11 days after completing the tablet course.

Graph II indicates the second oestrogen peak in 17 ovulatory cycles. In 12 cycles this occurred from 21 to 28 day of the cycle. In two cycles this peak occurred on 35th to 39th day of the cycle. The second oestrogen peak was ranging from 12  $\mu\text{g}$  to 50  $\mu\text{g}/24$  hours and in most of the cycles this peak was from 20 to 50  $\mu\text{g}/24$  hours.

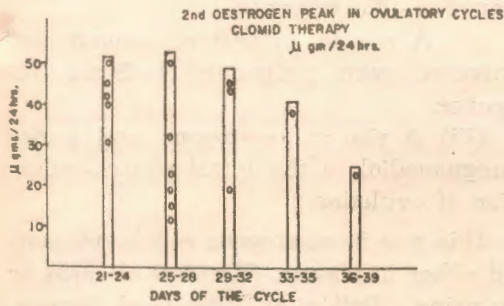


Fig. 2

Graph III indicates the oestrogen peak in 10 anovulatory cycles. The urinary oestrogen levels were varying from 16  $\mu\text{g}$  to 42  $\mu\text{g}/24$  hours and most of the oestrogen peaks were from 25-40  $\mu\text{g}/24$  hours. Four oestrogen peaks occurred on days 8-12 in these cycles compared to only one oestrogen peak at this time in ovulatory cycles.

Graph 4 indicates the serial oestrogen levels in three anovulatory cycles having no oestrogen peak. These cycles were

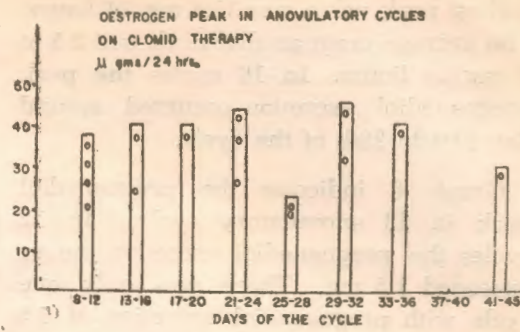


Fig. 3

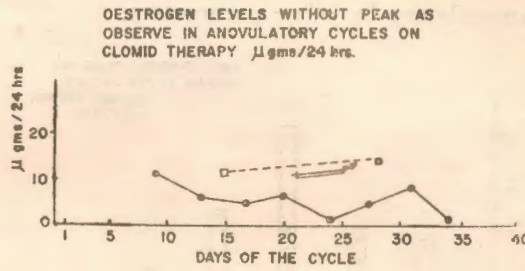


Fig. 4

having flat oestrogen curves indicating no response to the drug. All these values remained around 5 to 12  $\mu\text{g}/24$  hours.

Graph 5 indicates the pregnanediol peak in 21 ovulatory cycles. In 17 cycles the peak pregnanediol value was 2.5 mg/24 hours or more. In only 4 cycles the peak pregnanediol was 2  $\mu\text{g}/24$  hours. The

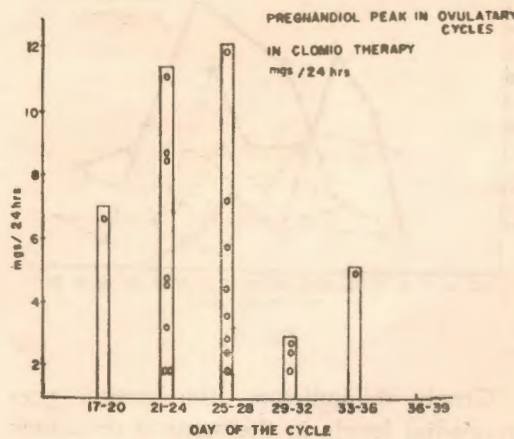


Fig. 5

highest peak value was 11.8 mg/24 hours. The average pregnanediol peak was 2.5 to 7 mg/24 hours. In 16 cycles the peak pregnanediol excretion occurred around day 21st to 28th of the cycle.

Graph 6 indicates the pregnanediol peak in 13 anovulatory cycles. In 12 cycles the pregnanediol excretion never exceeded 1.5 mg. There was only one cycle with pregnanediol excretion of 2.5 mg/24 hours but still the cycle was anovulatory by other parameters.

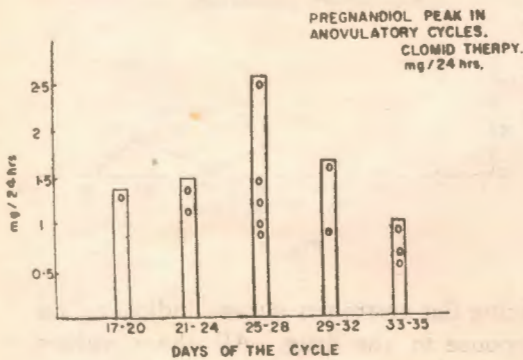


Fig. 6

Graph 7 indicates the serial oestrogen levels in six ovulatory cycles.

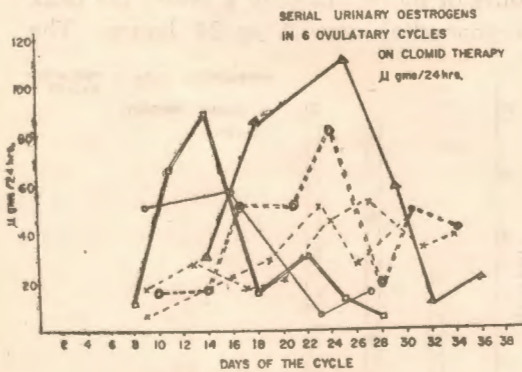


Fig. 7

Graph 8 indicates the serial pregnanediol levels in the same 6 ovulatory cycles.

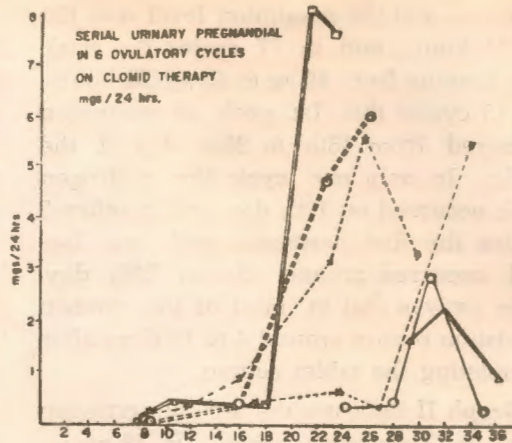


Fig. 8

Discussion

In properly selected cases on clomid therapy may show one of the following 3 types of response (Bell *et al* 1966):

- (i) No change in oestrogen and pregnanediol—No response.
- (ii) A rise in oestrogens without any increase with pregnanediol—Some response.
- (iii) A rise in oestrogens and a rise pregnanediol in the luteal phase—induction of ovulation.

This rise in oestrogens can be measured either in plasma (Kjeld *et al* 1975) or in urine (Bell *et al* 1966 Goebelsmann, 1975) According to Goebelsmann 24 hours urinary oestrogens represent the average oestrogen production more correctly than the plasma oestrogens. Plasma oestrogens fluctuate more rapidly. However, while monitoring exogenous gonadotrophins therapy, Plasma oestrodiol is the direct ovarian signal and is a better guide for planning the dosage. In all other cases 24 hours urinary oestrogens are as valuable as plasma oestrogens.

Pennington (1969) recorded a considerable rise in the excretion of oestrogens in almost all the cases who respond-

ed clomiphene citrate. They also observed that in ovulatory cycles with clomiphene therapy, the urinary oestrogens reached a level mostly above 30  $\mu\text{g}/24$  hours and the pregnanediol output in excess of 2 mg/24 hours on 23rd or 24th day of cycle. The minimum and the maximum urinary oestrogens peak in our cases were 30  $\mu\text{g}/24$  hours and 130  $\mu\text{g}/24$  hours. But the majority of ovulatory cycles demonstrated the peak urinary oestrogen values between 40-80  $\mu\text{g}/24$  hours. This oestrogen peak occurred in 13th to 20th day of the cycle. The second oestrogen peak in most of the ovulatory cycles was from 20-50  $\mu\text{g}/24$  hours and mostly occurred on 28th to 35th day of the cycle.

Delayed oestrogen peaks in some ovulatory cycles on clomid therapy are recorded by Bell *et al* (1966).

Anovulatory cycles with clomid therapy also showed a rise in urinary oestrogen levels ranging from 25-40  $\mu\text{g}/24$  hours in most of these cases. This shows a partial response to clomiphene citrate. Bell *et al* (1966) have also recorded a rise in urinary oestrogens as high as 80-90  $\mu\text{g}/24$  hours in anovulatory cycles with clomid therapy.

No response to clomiphene was demonstrated in 3 of our cases.

Most of our ovulatory cycles had a peak pregnanediol levels 2.5-7 mg/24 hours. But urinary pregnanediol of 2 mg/24 hours was recorded in 4 ovulatory cycles. Kjeld *et al* (1975) have stressed the importance of hormonal responses to the first course of clomid. However, some of our cases responded in the first or second cycle therapy but then failed to respond in the subsequent cycles.

According to Kjeld *et al* (1975) record, a considerable higher peak of plasma pregestenone in clomiphene induced ovulatory cycles compared to the spontaneous ovulatory cycles.

#### Summary

(i) Serial urinary oestrogen and pregnanediol values were studied in 19 women in 34 cycles on induction of ovulation with clomiphene citrate.

(ii) The 1st oestrogen peak was 40-80  $\mu\text{g}/24$  hours in most of the 21 ovulatory cycles around day 13th to 20th. The 2nd oestrogen peak was 20-150  $\mu\text{g}/24$  hours.

(iii) The peak pregnanediol excretion was 2.5 to 7 mg/24 hours and occurred around 21st to 28th day of the cycle.

#### Acknowledgement

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