



## Mid-luteal phase plasma progesterone levels in spontaneous and clomiphene citrate induced conception cycles

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**OBJECTIVE(S) :** To study the mean progesterone levels in mid-luteal phase in conception cycles, both spontaneous and clomiphene citrate induced.

**METHOD(S):** A record of 210 cases of primary infertility were analysed. Sixty of them had regular menstrual cycles (cycle length 26-35 days) and 150 had oligomenorrhoea (cycle length >35 days). To detect the ovulatory status, these 60 cases were advised to test for mid-luteal phase plasma progesterone levels (day 21-day 23). Nineteen of these women were found to have conceptive menstrual cycles on follow up with the blood reports (Group A). Out of 150 cases with oligomenorrhoea, 23 cases of polycystic ovarian syndrome (PCOS) conceived in the first cycle of treatment with clomiphene citrate for induction of ovulation (Group B). Serum progesterone levels were measured 7-9 days after documented ovulation by follicular study with ultrasonography.

**RESULTS :** Mean progesterone levels in Group A and Group B were  $17.11 \pm 5.30$  ng/mL and  $23.94 \pm 17.07$  ng/mL respectively. Statistical analysis showed that the difference in these values were significant.

**CONCLUSION(S):** Mean mid-luteal phase progesterone level in spontaneous conception cycle is significantly lower than that in clomiphene citrate induced conception cycle.

**Key words :** mid-luteal progesterone levels, conception cycle

### Introduction

Elevations in serum levels of progesterone is an indirect evidence of ovulation. The lower limits of progesterone levels in the luteal phase vary among laboratories but a level of more than 3 ng/mL confirms ovulation <sup>1</sup>.

In a regularly menstruating woman, the mid-luteal phase (typical day 21-23) is the period of peak progesterone secretion from the corpus luteum and the serum progesterone level remains at a fairly constant high level <sup>2</sup>.

Since the progesterone has a pulsatile secretion pattern, low level in a single study may not always imply ovulatory disturbance. It is important to avoid measuring progesterone level in serum too late when the level might have risen due to the effect of chorionic gonadotrophin from the implanted embryo. If measured too early, the level may be low. So timing of measurement of progesterone level in the luteal phase is important.

Many of the reference value guidelines were developed in women with supposedly normal ovulation and these measurements were not always in actual conception cycles. While a general ideal range for mid-luteal phase progesterone level is known, the mid-luteal progesterone level which is compatible with conception in a woman is not known and more so in a woman undergoing induction of ovulation with clomiphene citrate (CC).

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The purpose of the present study was to examine this issue.

## Methods

The records of 210 patients reporting with primary infertility were analysed. There were 60 women who had regular cycles (cycle length 26-35 days) and 150 women who had oligomenorrhic cycles (cycle length > 35 days). The 60 women with regular cycles had their mid-luteal phase progesterone levels measured (day 21-23) to assess their ovulatory status initially. Twenty-one women out of these 60 conceived in the tested cycle. Two of them had blighted ovum possibly due to corpus luteum deficiency and hence were not included in the study. Nineteen women continued with pregnancy (Group A) out of which 9 had already delivered singleton live babies and 10 have delivered subsequent to the submission of this paper.

There were 23 oligomenorrhic women who were diagnosed as PCOS and underwent induction of ovulation with CC (100 mg per day from day 5 to day 9) and conceived in the first cycle of treatment (Group B). PCOS was diagnosed as per the criteria laid down by the revised guidelines of PCOS consensus workshop group<sup>5</sup>. All these women had follicular studies with sonography and serum progesterone level was measured 7-9 days after documented ovulation in each case. None of these women had any luteal support with either progesterone or human chorionic gonadotrophin. Out of these 23 women, 14 have already delivered singleton live babies and 9 are having ongoing pregnancies at the time of the writing. Any pregnancy continuing more than 12 weeks of gestation is considered as ongoing pregnancy.

Serum progesterone levels were measured with Elecsys 1010 – electrochemiluminescence Immunoassay (Roche lot no. 166 229-01

Thus the progesterone values were obtained in two groups of women—

1. Group A – Women having spontaneous conception (n=19).
2. Group B – Women conceived in the first cycle of treatment with clomiphene citrate (n=23).

## Results

Table 1 shows the characteristics of the two groups of women along with the progesterone levels in the conception cycles. Age-wise and body mass index (BMI) wise both the groups were similar but the progesterone values were significantly different.

**Table 1. Patient characteristics and the progesterone values.**

	AGE (years)	Bodymass index (kg/M <sup>2</sup> )	Progesterone level (ng/mL)
Group A (n=19)			
Mean ± SD	28.2 ± 3.21	23.8 ± 2.0	17.11 ± 5.30 <sup>a</sup>
Range/Median	(21-33/29)	(19-28/24)	(11.16-29.05/16.93)
Group B (n=23)			
Mean ± SD	27.8 ± 3.10	25 ± 2.71	23.94 ± 17.07 <sup>a</sup>
Range/Median	(22-34/28)	(20-31/24)	(8.7-80.0/20.1)

<sup>a</sup> Z value 1.645 Significant (Critical value at 95% level of significance 1.813)

## Statistical analysis

Natural conception-cycles in 19 women having average mid-luteal progesterone level of 17.11 ± 5.30 ng/mL and 23 cases of stimulated-conception cycles having average midluteal progesterone level of 23.94 ± 17.07 ng/mL, a testing of the Null Hypothesis,  $H_0$  (mean 1 = mean 2) against the alternative  $H_1$  (mean 1 not equal to mean 2), in order to test the efficacy of clomiphene administration and using the statistic Z for equality of sample means with appropriate standard error at 95% level of significance, the observed Z value comes to 1.813 where as at 95% level, Z value in the study is found to be 1.645. Therefore the calculated value falls in the critical region and there is no reason to accept the null hypothesis and, in other words, the efficacy of the drug (clomiphene) is significant in respect to progesterone level in the blood. Thus the rise in progesterone value in stimulated-conception cycles is statistically significant.

## Discussion

For most hormones in gynecology, it is important to establish the normal range. A conception (either natural conception or stimulated cycle conception) cycle implies not only production of a fertilizable haploid ovum capable of developing into a baby but also a receptive endometrium to favor implantation.

Most studies on mid-luteal progesterone assay were done in women with regular cycles who were assumed to have normal ovulation<sup>1,5,6</sup>. Some of these women already had achieved a full term pregnancy but progesterone level was not measured during the pregnancy cycle. Laboratories all over the world use different standards or technics for hormonal measurements and absolute normal values for the ovarian cycle are difficult to establish. Each laboratory must provide a range of normality for their population. The threshold values for normal and subnormal by any test should be based on clinically defined end-points. The only way to determine where a threshold value is located is to perform

the test in a large group of women and then to observe them for occurrence of pregnancy <sup>4</sup>.

In an era of evidence-based medicine, there is a need to determine the exact reference values for proper ovulation and luteal phase adequacy. This can be accomplished only by retrospective analysis of mid-luteal progesterone concentration measured during ovulatory cycles that resulted in full term pregnancies. In the present study, data of only those women who conceived in tested cycle were analysed.

Sallam et al <sup>7</sup> had commented that to obtain mid-luteal progesterone values in spontaneous conception cycles is difficult and necessitates a large cohort of subjects who are willing to have their mid-luteal plasma progesterone levels studied during every cycle until pregnancy is achieved. In this context, the present study involves 60 regularly menstruating women, out of which 19 women conceived in the tested cycle.

The present study shows that the average progesterone value in a single serum sample in the mid-luteal phase of a potentially fertile cycle was  $17.11 \pm 5.30$  ng/mL. The same value in clomiphene citrate-stimulated potentially fertile cycle was  $23.9$  ng/mL  $\pm 17.07$ . All these fertile cycles were having singleton pregnancies and the rise in progesterone level between the two groups was by a factor of 1.3. Obviously the rise is due to several follicles developing under the influence of clomiphene citrate. Hull et al <sup>2</sup> had reported that progesterone levels are raised by a factor of 1.5 after clomiphene use. Radwanska et al <sup>8</sup> found that progesterone value increased from  $9.0 \pm 5.9$  ng/mL to  $27.3 \pm 10.3$  ng/mL in conception cycles following clomiphene citrate with or without human chorionic gonadotrophin. They commented that single progesterone measurement in the mid-luteal phase is a useful guide in the management of ovulatory infertility.

The usage of these reference values may aid the clinician in the prediction of high quality embryo and optimum luteinisation, and aid in the prediction as to whether or not a pregnancy is likely to result. It can also guide the clinician for consideration of any luteal support, if needed.

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