

# Gonadotropin Levels in Clomiphene Citrate Challenge Test

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**OBJECTIVES** - To find out whether study of LH or LH:FSH ratio by clomiphene citrate challenge test can explain poor response to clomiphene citrate and to find out the FSH level indicative of adequate ovarian reserve status. **METHODS** - Ninety-nine cases of primary infertility having dysovulation (by basal body temperature charts and serum progesterone levels) underwent clomiphene citrate challenge test and their FSH and LH levels were studied on day 10 of the cycle. Serum progesterone level was studied in each case on day 22 or 23. A serum progesterone level of less than 10 ng/mL was considered as poor response to clomiphene citrate dosage. **RESULTS**- Out of the 99 patients, 13 conceived in the tested cycle and these acted as controls. Out of the remaining 86 cases, 38 showed poor response. Patients who showed poor response did not differ from the control group having adequate ovarian reserve in their LH and LH:FSH ratio. FSH level above 13.32 mIU/mL indicated diminished ovarian reserve status. **CONCLUSIONS** - Study of LH or LH:FSH ratio by clomiphene citrate challenge test in a general infertility clinic does not help in predicting adequate ovulatory response to clomiphene citrate. FSH level less than 13.32 mIU/mL may be considered as indicative of adequate ovulatory reserve status.

**Key words:** clomiphene citrate challenge test, ovulatory reserve

## Introduction

There is no doubt that LH is needed during the follicular phase when it acts synergistically with FSH to produce estrogen. But some patients may be overexposed to LH, either by spontaneous release or by stimulatory agents like clomiphene citrate/gonadotrophin and this can cause follicular atresia or defective folliculogenesis and luteal insufficiency, collectively labeled as dysovulation. In a general infertility clinic the first drug used to treat dysovulation is clomiphene citrate.

There are many studies on the significance of excess LH in the follicular phase but the questions are at what stage of folliculogenesis does this excess LH exert its effect and can a clomiphene citrate challenge test unmask this excess LH environment and also what is its importance in a general infertility clinic?

There are no definite standardized criteria for a normal LH range in induction with clomiphene in dysovulation. Clomiphene citrate challenge test (CCCT) has been established to assess the ovarian reserve status by studying the FSH level (100 mg of clomiphene citrate given from day 5 to day 9 of the cycle and then measuring the FSH level on day 10). It is known that diminished ovarian reserve status can lead to unsatisfactory response to stimulation with clomiphene citrate but it is difficult to explain why a woman has poor response to

clomiphene citrate in spite of having adequate ovarian reserve status. It is not clear whether abnormal LH output or excess LH in relation to FSH in response to clomiphene citrate is the reason for this. It is also not clear whether CCCT can unmask this environment.

The present study was done in a general infertility clinic to determine whether study of LH or LH: FSH ratio, following CCCT, on day 10 of the cycle can guide a generalist to predict poor response to clomiphene citrate.

## Material and Methods

One hundred thirty-seven cases of primary infertility reporting for evaluations from May 2000 to April 2001 were asked to maintain basal body temperature chart for two months and those having regular cycles (26-32 days) were asked to measure serum progesterone level on 22<sup>nd</sup> or 23<sup>rd</sup> day in the second month. Those patients having oligomenorrheic cycles (cycle length more than 35 days) maintained only the basal body temperature chart for two months. Progesterone level of less than 10 ng/ml was considered to be indicative of dysovulatory state'. Out of these 137 women, 99 were found to be having dysovulatory cycles (41 had regular cycles and 58 had oligomenorrheic cycles) by elevated monophasic temperature patterns.

Because of their dysovulatory state, all these 99 women were advised to undergo CCCT (clomiphene citrate 100 mg given from 5<sup>th</sup> to 9<sup>th</sup> day) and serum FSH and LH were measured on the 10<sup>th</sup> day and serum progesterone on the 22<sup>nd</sup> / 23<sup>rd</sup> day of the same cycle.

Out of these 99 cases, 13 conceived in the same cycle and they acted as controls. Out of the remaining 86 cases, 38

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showed serum progesterone level less than 10ng/ml in the tested cycle indicating poor response (study group) inspite of stimulation with clomiphene citrate.

## Results

Table I shows the number of patients with regular cycles and those with oligomenorrhea who conceived in the same cycle. Out of 99 cases, 13 conceived in the first cycle of treatment with clomiphene citrate (test cycle)

and 38 showed poor response to the dose of clomiphene citrate given.

Table II shows the clinical details of the two groups of patients (control and the study group). There were no statistically significant differences between the values of any parameter in the two groups. Correlation coefficients between LH and LH FSH ratio in the control and study groups were - 0.212 and +0.756 respectively.

Table I : Type of menstrual cycle vis-a-vis response to clomiphene citrate

No. of Cases	Conceived in the test cycle (control group)	Poor response (study group)
Regular cycles (n=41)	2	13
Oligomenorrhic Cycles(n=58)	11	25
Total number (n=99)	13	38

Table II : Clinical and hormonal parameters

Parameters	Control Group		Study group	
	Mean (SO)	Median	Mean (SO)	Median
Age (years)	28.23	28	28.63	28
EMI	24.8 (2.77)	24	25.39 (3.31)	25
FSHmIU/mL	7.54 (2.89)	7	6.52 (2.46)	6.75
LHmIU/mL	10.47 (4.84)	9.5	9.45 (4.25)	9.75
LHFSH	1.56 (0.72)	1.5	1.58 (1.09)	1.30
Progesterone (ng/mL)	18.33 (6.90)	18.6		

SO -Standard Deviation

Correlation coefficient between LH and LHFSH in the control and study group was - 0.212 and +0.756 respectively.

## Discussion

Laboratories all over the world use different standards or techniques for hormonal measurements and absolute normal values for the ovarian cycle are difficult to establish. The threshold values for a normal and abnormal test should be based on clinically defined end points. The only way to determine where a threshold value is located is to perform the screening test in a large group of patients and then observe the patients clinically to see who is able to conceive". It is important to keep in mind that establishment of a range of values which can be expected to be found by a given method for a population of normal persons is dependent upon a multiplicity of factors viz., the specificity of the method, the population tested and the precision of the method in the hands of the analyst. For these reasons each laboratory should depend upon the range of expected values established by the manufacturer only until an in-house range can be

determined by the analyst using the method with a population indigenous to the area in which the laboratory is located.

A traditional approach to the management of infertility can be found in any textbook but it is important to stratify the care provided by a generalist using limited resources and those provided by an infertility / reproductive medicine subspecialist.

A large number of studies have appeared on the detrimental effects of LH in the follicular phase in both stimulated and natural cycles. It is claimed by many that pure FSH or recombinant FSH preparations would lead to better folliculogenesis and better quality of oocytes and finally higher pregnancy rates, but these are expensive. The questions are at what stage of folliculogenesis does the LH exert its effect and can a CCCT unmask this excess LH environment?

Serum progesterone concentration is higher than 5 ng/mL during the luteal phase. Most clinicians use the luteal phase progesterone level to establish both ovulation and the quality of ovulation. The precise threshold value of progesterone is controversial but most agree that a mid-luteal progesterone (6-8 days prior to the onset of menstruation - typically day 21-23 of the cycle) of less than 10 ng/mL is consistent with luteal dysfunction'. Swyer and Radwanska- reported that a single value of less than 10 ng/mL on day 22 or 23 of the cycle may be considered as deficient response to clomiphene dosage and is indicative of luteal insufficiency. So a deficient response to clomiphene citrate may indicate anovulation / poor folliculogenesis leading to luteal insufficiency.

The present study attempted to correlate the LH or LH:FSH ratio in poor responders. Soules et al" have found that compromised folliculogenesis is not a cause of luteal phase deficiency because the FSH levels were similar in the healthy women and women with luteal phase defects.

The mean FSH level in the control group of patients was 7.54 mIU/mL (SD 2.89). If we consider two SD above mean as indicative of diminished ovarian reserve as per criteria laid down by Navot et al<sup>5</sup> then the FSH value should be 13.32 mIU/mL. FSH value less than this may be considered to be indicative of adequate ovarian reserve status. In this study, the women in the poor responders group were well within the adequate ovarian reserve group. An abnormal CCCT has been found to have excellent predictive value for diminished ovarian reserve and poor long-term pregnancy rate during natural cycles, during ovulation induction and during IVF<sup>6</sup>. Watt et al, in an IVF program, found that women with FSH level more than 13.5 mIU/mL on day 10 following CCCT did not conceive at all.

Table II does not show any statistically significant differences between the various parameters studied between the two groups of women viz. responders and poor responders. Thus, the LH and LH:FSH ratio does not show any difference between the two groups. The correlation coefficients between the LH and LH:FSH ratio in the control group being - 0.212 and in the study group being +0.756, no definite correlation exists between individual LH value or LH:FSH ratio and poor response to clomiphene citrate. Thomas et al" have also concluded that follicular phase LH concentrations do not predict IVF fertilization rate or clinical outcome and are not clinically useful in an individual patient's management.

Thus, CCCT can be used to assess the ovarian reserve status only (in the present study the cut off level of FSH being 13.32 mIU/mL) and LH or LH:FSH ratio following CCCT carries no significance in predicting adequate ovulatory response to the standard dose of clomiphene citrate. Hedon et al<sup>7</sup> had stated that the decline in fecundability can be detected by FSH level on CCCT and it is reliable enough to be used as a screening test.

There is a real need to develop other methods to evaluate objectively the chance of an individual patient to have a satisfactory ovulatory response to clomiphene that can be appropriate for a general infertility clinic.

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