Clomiphene Citrate Challenge Test in Dysovulatory Infertility

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OBJECTIVE - To assess the relationship of LH : FSH ratio following clomiphene citrate challenge test (CCCT) with clinical pregnancy rate after treatment with clomiphene citrate in dysovulatory infertility. **METHOD –** Data of 156 cases of primary infertility due to dysovulation having CCCT and treatment with clomiphene citrate for six months were analysed and the clinical pregnancy rate obtained were studied. **RESULTS –** Maximum pregnancy rate was obtained when the LH: FSH ratio was between 1.2:1 and 1.4:1 followed by that when it was 1.5:1 and 1.7:1. No pregnancy occurred when the ratio was <0.5:1 and >2:6:1. Median value for the LH: FSH ratio for maximum conception rate was 1.395:1(SD ± 0.33). **CONCLUSION –** LH:FSH ratio in the CCCT can predict clinical pregnancy rate in dysovulatory infertility and the maximum success rate is obtained at the median value of 1.395:1 (S.D. ± 0.33)

Key words – LH: FSH ratio, clomiphene citrate challenge test, clomiphene citrate

Introduction

Clomiphene citrate challenge test (CCCT) has been reported to be a reliable indicator of ovarian reserve status. CCCT be easily performed and assessed in a clinical setting in any infertility clinic. Clomiphene can unmask any latent microendocrinopathy at the pituitary-ovary axis level which may not always be detectable by basal hormonal measurements as it is a stimulatory agent for gonadotrophins and is under a feedback control directly from the ovary.

The present study attempts to analyze the relationship between the clinical pregnancy rate and the LH: FSH ratio obtained by CCCT and to find an approach providing the maximum success.

Material and Methods

Data of 156 cases of primary infertility due to dysovulation from 1st January, 1999 to 31st December, 1999 were retrospectively analysed. At the initial visit they were asked to record the BBT (basal body temperature) for two to three months and the pattern of temperature graph was noted in each case. Only those cases where there were persistent "dysovulatory" changes (as per recommendation of Chattopadhyay et al[1]) were considered for clomiphene citrate therapy. On clinical examination there was no evidence of fibroid/ endometriosis pelvic inflammation in any case. Routine seminal analysis was normal in every case. Age group of the patients ranged between 25 to 38 years.

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In the first month of treatment a CCCT was done in each case (as a method of assessment of ovarian reserve)[2]. Clomiphene citrate 100 mg per day was given from day 5 to day 9 as treatment of the dysovulatory problems for a period of six months and the clinical pregnancy rate obtained was noted and CCCT the LH:FSH ratio was calculated. FSH and LH were estimated by ELISA method. All these cases had< 12 miu/ml serum FSH on day 10 .

Results

Out of the 156 cases at the end of six months 59 (37.8%) were pregnant. Table – I shows the number of cases and the number of pregnancies occurring in the various categories of LH : FSH ratio. The maximum number of pregnancies occurred when the LH: FSH ratio ranged between 1.2:1 and 1.4:1 followed by when it ranged between 1.5:1 and 1.7:1. It also shows the cumulative frequency distribution and based on it and covering the entire range from 0.3:1 to 2.9:1 of LH: FSH, the Median is found to be 1.395:1 (S.D ± 0.33) indicating highest incidence of pregnancy in the present series has occurred at that value.

Discussion

Laboratories all over the world use different standards or techniques for hormonal measurement; absolute "normal" values for the ovarian cycle are difficult to establish.

Each laboratory must provide a range of normality for their population. It is therefore suggested that the ratio of LH:FSH, instead of going by the absolute values, may assist in determining dysovulation. The threshold values for a normal and subnormal test should be based on clinically defined end-points. All the published

studies to date are observational in nature. 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 to observe them for occurrence of pregnancy[2].

A traditional approach to the management of infertility can be found in any standard textbook but it is important to stratify the care provided by an average gynecologist using limited resources and that provided by an "infertility / reproductive-endocrinologist" sub-specialist.

The present study aimed to assess clomiphene citrate by the achievement of pregnancy at the end of six months of treatment. We found that the success rate was highest when the L H F S H ratio by C C C T was between 1:2:1 and 1:4:1 followed by 1:5:1 and 1:7:1.

Sharara and Scott[3] have stressed the importance of C C C T over measurements of the basal hormonal levels. In any clinical setting, C C C T can be routinely performed.

In the present series the overall pegnancy rate was 37.8%. Gysler et al[3] and Hammond et al[4] had reported pregnancy rate of 40%.

In the present series the does of clomiphene citrate was kept constant at 100mg. / day because this is the does recommended for performing C C C T and F D A has recommended a maximum does of 100mg. / day[5]. In fact Rust et al[6] have found that more than 70% of the conceptions occur at does no higher than 100mg. / day for 5 days.

Clomiphene can produce four different types of responses - 1) absence of follicular recruitment and development 2) absence of appropriate ovulatory stimulus 3) normal ovulation with abnormal end organ effects and 4) normal ovulatory pattern and end organ function with persistent infertility. It is not clear whether the inability to respond appropriately to C C is a function of the properties of CC or is related to the etiology of dysovulation.

Chappel and Harles have suggested that abnormal follicular endocrinology brought about by inappropriate L H exposure may be an important factor in reproductive failures not only in women undergoing treatment with fertility drugs but also normal women. They further suggest that the presence of abnormally high levels of L H manifested by a clinical condition or induced or exaggerated by the administration of drugs is associated with poor quality of oocytes and lower embryonic viability. They also suggest that the resting levels of L H are adequate for normal follicular maturation and successful ovulation induction should employ techniques that elevate serum F S HH but not L H. One may envisage the role of L H during the follicular phase to be a crescendo - of little importance during the early follicular phase and most important at the time of ovulation. F S HH on the other hand has a reversed pattern of importance - essential for early events and having a relatively minor role at the time of ovulation. Hammond et al[8] have found that during the follicular phase under the F S H action the granulose cells begin to synthesize L H receptors and also LGF-1 (insulin like growth factor-1). The latter further stimulates follicular growth and expression of the aromatase enzyme system in the follicular apparatus. Again, F S H - induced "Inhibin" from the granulosa cells has the capacity to synergize with L H to stimulate the production of androgens from the theca cells[9]. Thus a balance has to be maintained between F S H and L H in the follicular phase at every stage.

It has been found that <1% of L H receptors need to be occupied to elicit a maximal steroidogenic response in the follicular phase[7] .L H has a pulsatile pattern of secretion and there could be differences in bio-activity and immunactivity of L H. But this differentiation is not possible in clinical practice neither is the analysis of L H - pulsatility. Thus the relatively high L H in comparison to F S H in response to clomiphene can cause a state of relative F S H deficiency and may affect the follicular microenvironment by increasing the abdrogenic milieu. The principle of using clomiphene citrate in dysovulation is to stimulate the recruitment of a cohort of preovulatory follicles and hence supernumerary oocytes[10]. This is also associated with steroidogenesis by the cohort of the follicles, Any perturbations in the output of the two gonadotrophins can desynchronize the whole ovulatory sequences and also the closely related endometrial maturation. F S H and L H arte secreted in a co-ordinated fashion to regulate follicle growth, ovulation and maintenance of the corpus luteum. Amount of estradiol produced depends on the relative exposure to each of the gonadotrophins once the minimal effective doses of gonadotrophins have been achieved[11]. Follicles with a diameter of <8mm show a relatively low intrafollicular oestrogen androgen ratio. From the midfollicular phase onwards, this ratio is reversed. Follicles destined to atresia have a higher androgen: estrogen ratio. There are evidences for follicle size-related, cycle-time related differences in the gonadotrophins levels in the follicles. Antral fluid levels of FSH and estrogens correlate positively[11]. Data are consistent with the concept that hormone concentrations are regulated in the microenvironment of the individual follicle.

Moreover a functional role has been imputed to the hormonal composition of the microenvironment[12]. The present study attempt to utilize the CCCT as a test for assessing the success rate in treatment with clomiphene citrate by studying the LH:FSH ratio and it can act as a guideline to stratify the patient and counseling the couple.

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Table I : LH:FSH Ratio and Pregnance Rate

LH : FSH ratio	No. of cases	No. Pregnancy (%)	Cumulative Frequency
0.3:1 – 0.5:1	2	0	0
0.6:1 – 0.8:1	10	1 (10 %)	1
0.9:1 – 1.1:1	13	5 (38.5 %)	6
1.2:1 – 1.4:1	50	24 (48 %)	30
1.5:1 – 1.7:1	44	189 (40.9 %)	48
1.8:1 – 2.0:1	21	7 (33.3 %)	55
2.1:1 – 2.3:1	12	3 (25 %)	58
2.4:1 – 2.6:1	4	1 (25 %)	59
2.7:1 – 2.9:1	1	0	59
Total	156	59	

Median LH:F.S.H. – 1.395:1 (S.D ± 0.33)

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