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Original Research Article

The effect of baseline serum luteinizing hormone levels on follicular development, ovulation, conception and pregnancy outcome in infertile patients with polycystic ovarian syndrome

Deepa Shanmugham*, R. K. Vidhyalakshmi, Shivamurthy H. M.

Department of Obstetrics and Gynecology, Aarupadai Veedu Medical College, Pondicherry, India

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***Correspondence:**

Dr. Deepa Shanmugham,

E-mail: drdeepabalamurugan@gmail.com

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ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder in infertile women. Raised tonic levels of luteinizing hormone (LH) is one of the main endocrinological disturbances in PCOS patients. Objective of present study was to evaluate the effect of baseline serum luteinizing hormone levels on follicular development, ovulation and conception and pregnancy outcome in infertile patients with PCOS.

Methods: This is a prospective study conducted on 50 consecutive infertile patients with PCOS. Baseline Day 2 serum luteinizing hormone concentration was done in selected patients. Ovulation induction was done with clomiphene citrate 100 mg from Day 3 to Day 7 of the cycle. Then patients were monitored for follicular development, ovulation, conception and early pregnancy loss.

Results: The mean age of the patients is 25 ± 3.6 yrs. The average duration of infertility is 5.4 yrs (2-10). The mean basal serum LH concentration in patients who ovulated was significantly low (5.6 IU) in comparison with patients who did not ovulate (10.1 IU). The mean basal serum LH concentration in patients who conceived was 3.9 IU in comparison with patients who did not conceive (5.9 IU) which was statistically significant ($p=0.04$). Out of 15 patients who conceived, 3 patients (20%) had early pregnancy loss.

Conclusions: Tonic hyper secretion of LH results in premature oocyte maturation, causing the problems with fertilization and miscarriage. Inappropriately raised LH appears to have deleterious effects on the pregnancy outcome.

Keywords: Infertility, LH, Ovulation, PCOS

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder in infertile women. Infertility affects 40% of women with PCOS.¹ Polycystic ovary syndrome (PCOS), a relatively common reproductive endocrine disorder often associated with high endogenous LH secretion, menstrual cycle disorders, infertility and high rates of spontaneous abortion, was considered the paradigm condition that proved the potential untoward actions of LH.

Raised tonic levels of luteinizing hormone (LH) is one of the main endocrinological disturbances in PCOS patients.² This inappropriate secretion of LH seems to affect both fertility and pregnancy outcomes of PCOS women. Increased production of androgens associated with high LH concentrations, coupled with their inefficient aromatization to estrogens related to the low FSH levels in PCOS patients, results in local androgen excess and oestrogen deficit within the ovary.³ This would constitute a potent androgenic environment for the follicle leading to cessation of follicular growth. This

forms the basis for the cause of infertility in patients with PCOS i.e., chronic anovulation.

Several investigators have reported that increased LH levels significantly reduced the fertilization and cleavage rates.^{4,5} In spite of all these if pregnancy is established, higher rates of miscarriage are reported by few authors.⁶

However, few literatures are available on effect of high tonic levels of luteinizing hormone on folliculogenesis and ovulation. The aim of our study is to evaluate the effect of baseline serum luteinizing hormone levels on follicular development, ovulation and conception in infertile patients with Polycystic Ovarian Syndrome.

METHODS

This is a prospective study conducted in the department of obstetrics and gynaecology from July 2016 to June 2017 in a tertiary care centre after obtaining Institutional Ethics Committee clearance. 50 consecutive infertile patients with polycystic ovarian syndrome (PCOS) attending the infertility clinic were enrolled for the study. The exclusion criteria was tubal factor infertility, male factor infertility, endometriosis and women with other endocrine problems like hypothyroidism and hyperprolactinemia. A detailed history and gynaecological examination was done in all patients.

Baseline Day 2 serum luteinizing hormone concentration (World Health Organisation international reference preparation code number 68/40) was done in all selected patients. Basal Day 2 Transvaginal Ultrasound pelvis (Mindray Z 5) was done to measure the endometrial thickness and to rule out ovarian cyst if any.

Then, ovulation induction was done with clomiphene citrate 100 mg from Day 3 to Day 7 of the cycle. Subsequent follicular monitoring was done by transvaginal sonogram from Day 9. Ovulation trigger with injection hCG 10,000 IU was done once the follicle reaches 18-20mm size. Ovulation was detected by transvaginal sonogram by the visualisation of crumpled follicle and presence of free fluid in POD. Ovulated patients were advised to review after 15 days for the confirmation of pregnancy.

Pregnancy was confirmed by detection of HCG in urine and appearance of gestational sac in ultra sonogram. Patients who conceived were followed up for antenatal care. Statistical analysis was done with student t test.

RESULTS

50 patients were enrolled for the study and among them 2 patients lost follow up.

Table 1 shows the demographic characteristics of the 48 study patients. The mean age of the patients is 25±3.6. The mean BMI of the patients is 27±2.2. The average

duration of infertility is 5.4 years (Range: 2-10 years). Out of 48 patients, 43 patients presented with primary infertility (89%) whereas 5 patients (11%) presented with secondary infertility. 75% of the patients presented with clinical features of hyperandrogenism like hirsutism and acne.

Table 1: Demographic characteristics of study patients.

Parameter	Value/Percentage
Mean Age	25±3.6 years
Mean BMI	27±2.2
Duration of infertility	5.4 years (2-10 years)
Primary infertility	43 pts (89%)
Secondary infertility	5 pts (11%)
Hyperandrogenism	75%

Table 2 and 3 shows basal serum LH concentration in each group. Out of 48 patients, 27 patients (56%) had good follicular development ovulated. Similarly, among 27 patients who ovulated and 15 patients (55%) conceived.

Table 2: Comparison of mean base line serum LH concentration of patients based on ovulation.

	Group A (Patients who ovulated) n = 27	Group B (Patients who didn't ovulate) n = 21	P value
Mean basal serum LH	5.6 IU/L	10.1 IU/L	0.0015
Range	2.1-10.2 IU/L	6.3-19 IU/L	

Table 3: Comparison of Mean base line serum LH concentration of patients based on conception.

	Group C (Patients who conceived) n = 15	Group D (Patients who didn't conceive) n = 12	P value
Mean basal serum LH	3.9 IU/L	5.9 IU/L	0.04
Range	2.1-5.6 IU/L	2.6-10.2 IU/L	

Statistical analysis was done with student t test (one tailed hypothesis) with significance level of 0.05. During the result analysis, patients were divided into those who ovulated (Group A) and who did not ovulate (Group B).

The basal serum LH concentration was compared in these 2 groups. The mean basal serum LH concentration in patients who ovulated (n=27) was 5.6 IU/lit (2.1-10.2) in comparison with patients who did not ovulate (n=21) which was 10.1 IU/lit (6.3-19) and the difference was statistically significant, t value= -3, p value = 0.0015 (p<0.05). Similarly, patients who ovulated were divided into patients who conceived (Group C) and who did not (Group D). The mean basal serum LH concentration in

patients who conceived (n=15) was significantly low [3.9 IU/lit (2.1-5.6)] in comparison with patients who did not conceive (n=12) which was 5.9 IU/lit (2.6-10.2) [t value=-1.74, p value=0.04 (p<0.05)]. Among the 15 patients who conceived, 3 patients had early pregnancy loss (20%).

DISCUSSION

In 1935, Stein IF et al first described a symptom complex associated with anovulation.⁷ They described 7 patients with amenorrhea, hirsutism and enlarged polycystic ovaries. They reported that all seven resumed menses and that two became pregnant after bilateral wedge resection of ovaries. They speculated that the thickened ovarian capsule prevented follicles from reaching and escaping from the surface of the ovary.

The diagnosis of polycystic ovarian syndrome is based on Rotterdam's criteria 2003.⁸ Two of the three following criteria are required for diagnosis.

- Menstrual abnormalities like amenorrhea, oligomenorrhea.
- Hyperandrogenism- clinically by acne, hirsutism or laboratory elevated testosterone levels.
- Polycystic appearance of ovaries on ultrasound, containing multiple small follicles measuring 2-9 mm size.

The pathophysiology responsible for development of polycystic ovaries has puzzled gynaecologists and endocrinologists for many years and proven very difficult to define.

Compared to normally cycling women, those with PCOS generally exhibit increased serum LH concentrations, low-normal FSH levels and increased LH: FSH ratios. The increase in serum LH levels results from abnormal LH secretory dynamics, characterized by an increase in LH pulse frequency and to a lesser extent in pulse amplitude.⁹

The primary evidence indicating that excessive LH stimulation plays an important role in the pathophysiology of PCOS comes from examining the effects of treatment with GnRH antagonists and long-acting GnRH agonists. These observations suggest that excessive LH secretion or stimulation may be an important cause of disordered follicular development and anovulation.¹⁰

The present study was conducted to evaluate the deleterious effect of high concentration of serum LH on follicular development, ovulation, and conception and on developing fetus. The average BMI of the study patients was 26.4 who fall in the category of overweight which is comparable to the study by Adams et al.¹¹

Adams et al studied on mean LH concentrations of 54 women treated for 182 cycles and found that there was no significant difference between the basal LH concentrations of women who did and did not ovulate (14 versus 21, p=0.2). Basal luteinising hormone concentrations were significantly lower in those who conceived (12.4 IU/L) (Range 1.3-29 IU/L) than in those who did not 19 IU/L (3.5-50 IU/L) and in those whose pregnancy progressed 9.6 IU/L (1.3-29) than in those with early loss of pregnancy 17.9 IU/L (7.0-29.0).¹¹

Shoham also states that LH exhibits an important role in the development of the growing follicle and maturation of the oocyte. It also seems that hyper secretion of LH during the follicular phase implies adverse effects on the fertility process.¹² Homberg observed that impaired rates of fertilization, conception and miscarriage are obtained when LH levels are high before oocytes are collected, during ovulation induction or in women with regular cycles. He also concluded that Tonic hyper secretion of LH appears to induce premature oocyte maturation, causing the problems with fertilization and miscarriage.¹³

Regan investigated the relation between prepregnancy follicular-phase serum luteinising hormone (LH) concentrations and outcome of pregnancy was investigated prospectively in 193 women with regular spontaneous menstrual cycles. Of the 147 women with LH concentrations of less than 10 IU/l (normal LH group) 130 (88%) conceived, whereas only 31 (67%) of the 46 women with LH values of 10 IU/l or more (high LH group) did so. In the high LH group, 20 (65%) of the pregnancies ended in miscarriage, whereas only 15 (12%) of pregnancies in the normal LH group did so.¹⁴

Tariatzis concludes that in PCOS patients stimulated for IVF with HMG, follicular phase LH levels have an adverse effect on follicle and oocyte quality. Inappropriately raised LH appears to have a delirious effect on the pregnancy outcome.¹⁵

Kolibanakis et al found that a significant decrease of both ongoing pregnancy rate and implantation rate was present across groups of patients with increasing LH levels. The highest implantation rate and ongoing pregnancy rate was present in those patients with LH levels on day 8 of stimulation ≤ 0.5 IU/l.¹⁶ In another study by Howles C M et al, in women undergoing IVF treatment with a combination of CC and hMG, there were no pregnancies recorded if the urinary output of LH was elevated when measured two days prior to the day of hCG administration.⁵ Moreover, Stanger and Yovitch, have reported that high concentrations of luteinising hormone in the few days before oocytes were collected from women for in vitro fertilisation were associated with impaired rates of fertilisation and conception.⁴

Polycystic ovary syndrome is associated with hyper secretion of luteinizing hormone (LH) which has been implicated in the aetiology of early pregnancy loss.

Inappropriately raised LH levels may have adverse effects on the developing oocyte or endometrium either directly, or indirectly by causing an elevation in testosterone and oestrogen levels. In a case-control study done by Watson et al, 21 women with early pregnancy loss and 10 multiparous controls were investigated and found that 81% of cases and one of ten control subjects had polycystic ovaries. Seventeen women with pregnancy loss had either raised urinary LH excretion or a premature LH surge, one control subject had a premature LH surge. These data demonstrate abnormalities in LH secretion in 81% of women with recurrent fetal loss.¹⁷

In a study by Yi Ping Zhong et al in 2011, comparison of endocrine profile and IVF outcome in anovulatory PCOS patients, ovulatory PCO and normal ovaries was done. They found that PCOS patients with central obesity, high LH and insulin resistance exhibited highest abortion rate.¹⁸

Humaidan et al studied the effect of LH levels on D8 of stimulation in terms of ovarian response and pregnancy outcome. They conclude that circulating levels of LH on D8 have a significant effect on ovarian response and subsequent pregnancy outcome in IVF. LH should be neither too low and nor too high for the successful ovarian response for the implantation.¹⁹

CONCLUSION

To conclude, Tonic hyper secretion of LH in infertile patients with polycystic ovarian syndrome results in disturbed follicular growth, poor quality of oocytes causing problems with ovulation and conception. However, further studies involving a larger sample is needed to prove the deleterious effect of hypertonic luteinizing hormone in PCOS.

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