Prognostic Value of Day 3 Luteinising Hormone (LH) in the prediction of Ovarian Response in Patients with Polycystic Ovary syndrome

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Abstract: Background: The aim of this study was to test the prognostic value of day 3 LH in predicting the success of ovarian response in patients with polycystic ovary syndrome. **Methods:** A prospective observational study was conducted at Infertility outpatient clinic, Sohag Teaching Hospital. Patients were sixity PCOS women who underwent induction of ovulation. All women had serum basal LH measured before induction of ovulation. The main outcome measured was ovarian response using folliculometry and serum progesterone. **Results:** PCOS women with LH < 8 mIU/ml had higher incidence of ovulation than those with LH>8 mIU/ml using both folliculometry and serum progesterone (44.73% vs 10.52%, P=0.01), also PCOS women with LH/FSH ratio <2 had higher incidence of ovulation than those with LH/FSH ratio>2 (40.9 % vs 7.69 %, P=0.026). **Conclusions:** Basal serum LH and LH/FSH ratio may has useful prognostic value in the prediction of ovarian response in patients with PCOS.
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Introduction:

Luteinizing hormone (LH) is a hormone released by the pituitary gland in response to luteinizing hormone- releasing hormone. It controls the length and sequence of the female menstrual cycle, including ovulation, preparation of the uterus for implantation of a fertilized egg, and ovarian production of both estrogen and progesterone.

Theca cells in the ovary respond to LH stimulation by secretion of testosterone, which is converted into estrogen by adjacent granulosa cells. In women, ovulation of mature follicles on the ovary is induced by a large burst of LH secretion - the preovulatory LH surge. Residual cells within ovulated follicles proliferate to form corpora lutea, which secrete the steroid hormones – progesterone and estradiol. Progesterone is necessary for the maintenance of pregnancy, and, in most mammals, LH is required for continued development and function of corpora lutea.

Both the absolute level of circulating LH and its relationship to FSH levels are significantly elevated in PCOS women as compared with controls. This is due to an increased amplitude and frequency of LH pulse.

Elevated LH concentrations (above the 95th percentile of normal) can be observed in ~60% of PCOS women, whereas the LH/FSH ratio may be elevated in up to 95% of subjects if women who have ovulated recently are excluded. LH levels may be influenced by the temporal relationship to ovulation, which transiently normalizes LH, by the BMI (being higher in lean PCOS women) and by the assay system used. The potential negative actions of LH on human reproduction are highly controversial. Some authors have suggested that high LH levels could have detrimental effects on oocyte maturity and fertilization as well as lower pregnancy and higher miscarriage rates.

However, other studies have shown no untoward actions of LH on oocyte and embryo quality, or on fertilization, implantation and pregnancy rates. Reduction of endogenous LH levels with GnRH agonists also provided conflicting results, as some studies have suggested that this maneouvre could reduce miscarriage rates, while others have questioned this therapeutic effect.

LH levels or the administration of exogenous LH were not found to affect the chances of ovulation or achievement of pregnancy using clomiphene citrate or exogenous gonadotropins. Based on the aforementioned data, the panel felt that measurement of serum LH levels should not be considered necessary for the clinical diagnosis of PCOS. LH levels could be useful as a secondary parameter (especially in lean women with amenorrhea, or in research.

LH pulse amplitude and frequency were increased in PCOS cases. Serum LH level is an

important parameter in PCOS, even though it is not included in the 2003 European Society for Human Reproduction (ESHRE)/American Society of Reproductive Medicine (ASRM) diagnostic criteria.

Elevated serum LH level has been thought to play a key role in ovulatory dysfunction in PCOS, however, an LH level is subject to change according to the days from menses or withdrawal bleeding. Both exogenous progesterone exposure and recent spontaneous ovulation transiently suppress LH secretion. Additionally, LH level and LH pulse amplitude negatively correlate with body mass index (BMI). Previous reports showed that LH hypersecretion plays an important role in PCOS with ovulatory disorder. LH levels and the LH/FSH ratio were elevated in 75% and 94% of patients with anovulatory PCOS, respectively. On the other hand, almost all normal cyclic women with PCO have a normal LH level and LH/FSH ratio.7.

The domestic PCOS criteria of the Japanese Society of Obstetrics and Gynecology (JSOG 2007) consist of the association of all three of the following factors: chronic anovulation, LH hypersecretion and/or hyperandrogenism and the LH level is influenced by some factors and altered according to the menstrual cycle and body condition.

LH levels were influenced by the days from menses or withdrawal bleeding, and that hormonal examination within 10 days from menses or withdrawal bleeding was not suitable for estimating LH hypersecretion of PCOS with anovulation or delayed ovulation. It has been reported that days from menses or withdrawal bleeding and BMI correlated with LH levels.

Both endogenous and exogenous progesterone seemed to suppress LH secretion. After ovulation or exogenous progesterone injection, LH pulse frequency, but not LH pulse amplitude, is reduced and both mean LH value and LH/FSH ratio are decreased.

These suppressive effects of progesterone on LH levels are continued to early phase in the next cycle. LH pulse amplitude also had a negative correlation with BMI, however some authors oppose this opinion. all subjects fulfilled the criteria, including LH hypersecretion (LH levels >7 and LH/FSH ratio >1), LH levels in patients with PCOS were strongly influenced by the days from menses or withdrawal bleeding. the late phase (more than 10 days after menses or withdrawal bleeding) is suitable for estimating the LH hypersecretion of PCOS.

2. Patients and Methods

Study design:

A prospective clinical trial included sixity PCOS women.

Setting and Timing:

Patients were recruited from Infertility outpatient clinic, Sohag Teaching Hospital between May 2016-May 2017.

Approval:

The protocol of the study was approved by Sohag University Department of Obstetrics and Gynecology Ethical Committee.

Inclusion criteria:

1- Criteria for diagnosis of PCOS **(ESHRE/ASRM):**

Two of the following:

- History suggesting of oligo-and/or anovulation.
- Clinical signs of hyperandrogism (hirsutism or acne).
- Polycystic ovaries by TVUS: (presence of 12 follicles or more in each ovary measuring 2-9mm in diameter and/or increase ovarian volume (>10ml).

2-Patients chosen were between 20-35 years old. (There is a correlation between extrems of age and ovarian function).

3-Body Mass Index (BMI) 20-30 kg/m2. (obese patients may show decreased ovulation).

4-Agreement for participation in the study.

5-Patients chosen didn't receive any hormonal treatment or induction of ovulation in the previous cycle prior to the targest study cycle.

Exclusion criteria:

1. Age > 35 and < 20 years old.
2. BMI > 30 and < 20 Kg/m2**.**
3. Patients refusing participation in the study.
4. Patients showing evidence of Hyper or hypothyroidism and Hyperprolactinaemia, these conditions may affect ovulation response.

5-Patients who recieved hormonal treatment or induction of ovulation in the previous cycle prior to the targest study cycle.

After a verbal consent all study participants were subjected to the following:

A. History taking:

Including symptoms of androgen excess such as acne or hirsutism, menstrual irregularities and medications for induction of ovulation.

B. Clinical examination:

- Height, body weight and BMI.
- Evidence of associated hirsutism or galactorhea.

C. Basal hormonal assay:

- Serum FSH, LH, E2, TSH and prolactin
- All samples were measured in the early follicular phase (day 3).
- PCOS patients presenting with amenorrhea were instructed to come on day 3 of a natural cycle. Patients who received hormonal therapy for withdrawal bleeding to start induction of ovulation

were excluded from the study in order to have an accutate estimate of basal LH.

- **Sample collection**

Fasting blood samples were taken from all women (5 ml) in the early follicular phase of menstrual cycle (day 3) and collected in Vacutainer tubes. All samples were kept at room temperature for at least 30 min to allow the blood to clot and were then centrifuged at 2000 for 15 min. Serum was collected and stored at -20° C until assayed.

- The concentrations of FSH, LH, E2, TSH and prolactin, were assayed using reagents supplied by Dpc (Diagnostic Products Corporation, 5700 west 96th st., Los Angeles) by enzyme chemiluminescence immunoassay.
- The study group will be divided into 2 groups based on the basal serum LH level: Group I: LH<8 **mIU/ml**, Group II:>8 **mIU/ml**. These values were be used to be consistent with previously published reports **(Noci et al.,1998, Mukherjee et al.,1996; Noci et al.,2000).**

D-Treatment Protocol and Follow up:

- All patients were given clomifene citrate 100 mg/day for 5 days starting from day 2 of the cycle and Metformin 500mg t.d.s.
- Follow up folliculometry:

Transvaginal ultrasound (TVUS) scan starting from day 10 and repeated every other day to detect the follicles greater than 16 mm in diameter apart from basal day 2 or day 3 TVUS prior to induction of ovulation.

- Two doses of 5000 IU of HCG were given to trigger ovulation when one follicle with a diameter of 16 mm or two to three follicles. Subjects were not given HCG if four or more follicles with diameters of 16 mm. by TVUS and not enrolled in our study.
- Serum progesterone: blood sample was taken 6–9 days after the HCG administration.

The concentrations of progesterone (mid-luteal) was assayed using reagents supplied by Dpc (Diagnostic products corporation, 5700 west 96th st., Los Angeles) by enzyme chemiluminescence immunoassay.

A concentration >10 ng/ml (>32 nmol/l) or higher was generally considered to be consistent with ovulation **(Moghissi, 1980; Coelingh Bennink et al., 1998; Sallam et al., 1999; Yarali et al., 1999; Hugues et al., 2005 and Arce., et al 2011**).

- Ovulation was considered satisfactory if the transvaginal u/s revealed a graph of at least one follicle at size of 16 mm or more with subsequent evidence of follicle rupture or mid-luteal progesterone >10 ng/ml or both.

E-Statistical Analysis

The data were coded, entered and processed on an IBM-PC compatible computer using SPSS (version 11). The level $P < 0.05$ was considered the cut-off value for significance.

The following tests were done:

- **Mean**
- **standard deviation (SD)**

Student's t-test was used to assess the statistical significance of the difference between two population means in a study involving **independent** samples.

3. Results:

The current study was conducted in Sohag Teaching Hospital. The study included sixty patients with polycystic ovary syndrome (PCOS).

Serum FSH, LH, Prolactin, E2 and TSH were checked for all the sixty PCOS patients on the third day of the menstrual cycle.

Three women with abnormal hormonal profile (hyperprolactinemia) were excluded from the study. Therefore, the study consisted of 57 women.

According to day 3 LH level, patients were divided into 2 groups: group I: LH<8 **mIU/ml** (38 patients) and group II: LH>8 **mIU/ml** (19 patients).

The demographic data of these patients were recorded in Table (3).

Table (1): Demographic data of the 2 groups

	group I (LH<8 mIU/ml) 38 cases	**group II (LH>8 mIU/ml) 19 cases**			
	Mean±SD	**Mean±SD**	**t**	**P**	**sig.**
Age (years)	26.15+4.18	27.13+4.96	-0.482	0.636	NS
BMI (kg/m2)	27.04+2.07	26.99+2.87	0.038	0.970	NS
Parity	1.15+1.28	0.25+0.46	1.905	0.172	NS
Duration of infertility (years.)	3.04+1.74	3 +2.07	0.046	0.964	NS

Student's t test

There was no statistical significant difference between two groups as regards the mean age, BMI, parity and duration of infertility P>0.05.

Table (2): Distribution of FSH, LH, Prolactin, E2 and TSH levels among the 2 groups

	group I (LH<8 mIU/ml) 38 cases	group II (LH>8 mIU/ml) 19 cases			
	Mean±SD	Mean±SD	t	P	sig.
FSH (mIU/ml)	6.67+1.39	7.29+3.40	-0.593-	0.633	NS
LH (mIU/ml)	5.83+1.32	14.93+5.38	-4.689-	0.002	**S**
LH/FSH RATIO	0.90+0.24	2.32+0.91	-4.271-	0.003	**S**
E2 (pg/ml)	59.68+14.22	59.74+23.38	-0.007-	0.636	NS
PROLACTIN (ng/ml)	13.39+8.16	14.14+8.78	-0.201-	0.843	NS
TSH (uIU/ml)	2.17+0.75	2.22+0.55	-0.167-	0.995	NS

Student's t test

Group II (LH >8 **mIU/ml**) showed a statistically higher mean LH/FSH ratio than those with Group I (LH <8 **mIU/ml**) P<0.05.

There was no statistical significant difference between two groups as regards the mean FSH, E2, prolactin and TSH P>0.05.

Table (3): Comparison between patients in Group I (LH <8 mIU/ml) and patients in Group II (LH ≥8 mIU/ml) as regard the incidence of ovulation.

	Group I (LH <8 mIU/ml) 38 cases	Group II (LH ≥8 mIU/ml) 19 cases	p-value	sig
Criteria for diagnosis of ovulation by folliculometry	22 57.89%	11 57.89%	0.117	NS
Criteria for diagnosis of ovulation by seum progesterone	17 44.73%	2 10.52%	0.010	**S**
Criteria for diagnosis of ovulation by both folliculometry and serum progesterone	17 44.73%	2 10.52%	0.010	**S**

Student's t test

There was no statistical significant difference between two groups as regards the incidence of ovulation using folliculometry alone P>0.05.

Group I (LH <8 **mIU/ml**) showed significant higher incidence of ovulation than group II (LH>8 **mIU/ml**) using serum progesterone alone and both folliculometry and serum progesterone p<0.05.

According to LH/FSH ratio, patients were divided into 2 groups: group A with LH/FSH ratio < 2 included 44 patients and group B with LH/FSH ratio> 2 included 13 patients.

Table (4): Comparison between patients with LH/FSH ratio<2 and patients with LH/FSH ratio>2 as regard the incidence of ovulation

	LH/FSH ratio<2 44 cases	LH/FSH ratio>2 13 cases	p-value	sig
Criteria for diagnosis of ovulation by folliculometry	28 63.63%	5 38.46%	0.106	NS
Criteria for diagnosis of ovulation by seum progesterone	18 40.9 %	1 7.69 %	0.026	**S**
Criteria for diagnosis of ovulation by both folliculometry and seum progesterone	18 40.9 %	1 7.69 %	0.026	**S**

Student's t test

The study showed that there is no significant higher incidence of ovulation in group A (LH/FSH ratio<2) compared with group B (LH/FSH ratio>2) using folliculometry alone P>0.05.

Group A (LH/FSH ratio<2) showed significant higher incidence of ovulation than group B (LH/FSH ratio>2) using serum progesterone and both folliculometry and serum progesterone P<0.05.

4. Discussion:

PCOS is defined by **ESHRE/ASRM** as the presence of any two of the following three criteria: (i) polycystic ovaries; (ii) oligo- /anovulation; and/or (iii) clinical or biochemical evidence of hyperandroginism. PCOS may be the leading cause of infertility **(Hoyt et al., 2004).** Clomiphene citrate (CC) is considered the

first-line treatment for infertile women with PCOS **(Saleh et al., 2004 and Yildiz et al., 2004)** However, 20% of patients have been shown to be resistant to CC **(Imani et al., 1998).**

Because androgen production by theca cells is LH dependant **(Erickson et al., 1985**), it would seem to follow that the elevated levels of LH seen in women with PCOS leads to increased ovarian androgen production and anovulation.

In this study we have investigated the relationship between basal serum LH and ovarian response in sixty PCOS patients in infertility outpatient clinic, Sohag Teaching Hospital between May 2016-May 2017.

Three women with abnormal hormonal profile (hyperprolactinemia) were excluded from the study. Therefore, the study consisted of 57 women.

In the current study we have no serious complications as ovarian hyperstimulation syndrome.

In this study the study group were divided into two groups group I (LH <8**mIU/ml**) 38 cases and group II (LH ≥8**mIU/ml**) 19 cases according to the serum luteinizing hormone (LH) levels.

In the current study ovulation was confirmed in 22 patients (57.894%) with LH < 8**mIU/ml** and in 11 patients (57.894%) with LH >8**mIU/ml** when detected by folliculometry and in 17 patients (44.736%) with LH < 8**mIU/ml** and in 2 patients (10.52%) with LH >8**mIU/ml** when detected by serum progesterone and in 17 patients (44.73%) with LH < 8**mIU/ml** and in 2 patients (10.52%) with LH >8**mIU/ml** when detected by both folliculometry and serum progesterone.

In the current study there was no statistical significant difference between two groups as regards the mean age, BMI, parity and duration of infertility P>0.05.

Group II (LH >8**mIU/ml**) showed a statistically higher mean LH/FSH ratio than those with Group I (LH <8**mIU/ml**) P<0.05.

There was no statistical significant difference between two groups as regards the mean FSH, E2, prolactin and TSH P>0.05.

There was no statistical significant difference between two groups as regards the incidence of ovulation using folliculometry P>0.05.

Group I (LH <8**mIU/ml**) showed significant higher incidence of ovulation than group II (LH>8**mIU/ml**) using serum progesterone and both folliculometry and serum progesterone p<0.05.

Kassab et al., reported that early follicular serum LH measurements in the 6 months before IVF/ICSI treatment cycle did not correlate with the clinical pregnancy or the live birth rate (P = 0.76) (P = 0.77) respectively in an observational study included 1333 consecutive women undergoing invitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) after adjusting for age, BMI, day of oocyte retrieval, starting dose, total dose of stimulation, type of gonadotrophin used, number of oocytes retrieved, fertilization rate and number of embryos transferred. **(Kassab et al.,2007).**

Also, **Bjercke et al., 2005** found that Serum LH concentration on stimulation day 1 cannot predict ovarian response, conception and pregnancy outcome in women receiving long-term down-regulation during assisted reproduction treatment.

Our result disagrees with **Thomas et al.,** who reported that basal LH modifies and improves the information given by basal FSH alone. Low FSH level combined with high LH probably reflects a well-preserved ovarian reserve and is associated with the highest success rates at IVF/ICSI in a prospective observational study included 745 women, who underwent 1328 IVF/ICSI treatment cycles reported that combinations of FSH and LH have significantly better information than the LH:FSH ratio, or each gonadotrophin alone: highest mean pregnancy rate (39%) was achieved in women with low FSH (6.7 U/l) and with high LH levels (.4.9 U/l), whereas pregnancy rate was lowest (22%) in women with high FSH and low LH levels. Pregnancy rates were intermediate (27–28%) if FSH and LH were either both low or both high (P for trend ¼ 0.0004). Associations to delivery rates and measures of ovarian response and embryo quality followed the same pattern. (**Thomas et al.,2009**).

Our study agrees with **Regan et al. and Homburg et al. 1998** who reported that women with PCOS having high LH levels have significantly lower rates of ovulation, fertilization and pregnancy when compared with normal LH levels of PCOS patients **(Regan et al., 1990 and Homburg et al., 1998).**

This also confirmed with **(Homburg et al. 1988)** prospective study which included 45 PCOS women reported that LH levels were lower in those who conceived vs. not conceived and reported that LH levels were higher in those who miscarried vs. continued pregnancy.

It also agrees with **(Regan et al., 1990)** in their prospective study which included 197 PCOS women with spontaneous ovulation reported that the group of patients who had (LH < 10 mIU/L) 88 % got pregnant with 12 % early pregnancy loss while the other group of patients who had (LH > 10 mIU/L) 67 %got pregnant with 65% early pregnancy loss.

In our study the study group were furthermore divided according to LH/FSH ratio into 2 groups: group A with LH/FSH ratio < 2 included 44 patients and group B with LH/FSH ratio> 2 included 13 patients.

Ovulation was confirmed in 28 patients (63.63%) with LH/FSH ratio < 2 and in 5 patients

(38.46%) with LH/FSH ratio>2 when detected by folliculometry and in 18 patients (40.9%) with LH/FSH ratio and in 1 patients (7.69%) with LH/FSH ratio> 2 when detected by serum progesterone and in 18 patients (40.9%) with LH/FSH ratio and in 1 patients (7.69%) with LH/FSH ratio> 2 when detected by both folliculometry and serum progesterone.

Group A (LH/FSH ratio<2) showed significant higher incidence of ovulation than group B (LH/FSH ratio>2) using serum progesterone and both folliculometry and serum progesterone $p<0.05$.

Group A (LH/FSH ratio<2) showed non significant higher incidence of ovulation than group B (LH/FSH ratio>2) using folliculometry alone $p>0.05$.

There is a disagreement with **Orvieto et al.,**2012 who found that the PCOS patients with LH/FSH ratio >2 achieved a non-significantly higher pregnancy rate using the GnRH-agonist (50% vs 17.9%, p = 0.2; respectively), as compared to the GnRH-antagonist protocols**. (Orvieto et al.,2012).**

There is an agreement with **Wiser et al.,** who found that PCOS patients with LH/FSH ratio of > 1.5 had decreased pregnancy rate than in those with a ratio of 0.5-1.5 (40.4%), $p < 0.05$. **(Wiser et al.,2013).**

Our study showed that there is a high degree of correlation between basal serum LH level and LH/FSH ratio estimation in predicting success of ovulation induction in PCOS patients. A basal LH level <8**mIU/ml** or an estimated LH/FSH ratio <2 had been associated with higher degree of successful ovulation had been assissted by both folliculometry and serum progesterone.

Although our study had evaluated for success of satisfactory ovulation using such parameter of LH assay and LH/FSH ratio yet our study had not extended for evaluation of clinical pregnancy rate because of necessity for extended follow up for several cycles which was not feasible for many of our patients.

Summary and Conclusions

This study shows that the basal serum LH and LH/FSH ratio may has useful prognostic value in the prediction of ovarian response in patients with PCOS. The value of instituting a routine measuring of serum LH and LH/FSH ratio before instituting chosen induction protocol in routine fertility and endocrinological conditions remain to be confirmed by further studies.

Our study recommends that strategies to suppress LH secretion in PCOS patients such as the use of oral contraceptives (OCP) before induction of ovulation may correlate with good ovarian response, conception and pregnancy outcome.

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