Original Article

Do basal Luteinizing Hormone and Luteinizing Hormone/Follicle-Stimulating Hormone Ratio Have Significance in Prognosticating the Outcome of *In vitro* Fertilization Cycles in Polycystic Ovary Syndrome?

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Abstract

Context: Tonic hypersecretion of luteinizing hormone (LH) appears to impact both fertility and pregnancy outcomes in women with polycystic ovary syndrome (PCOS). **Aim:** Whether high basal day 2/3 serum LH levels and day 2/3 LH/follicle-stimulating hormone (FSH) ratio affect *in vitro* fertilization (IVF) cycle outcomes in PCOS patients undergoing controlled ovarian hyperstimulation using gonadotropin-releasing hormone (GnRH) antagonists. **Settings and Design:** A retrospective cohort study was conducted in Assisted Reproductive Technique Center, Department of Obstetrics and Gynaecology, at a tertiary care institute, on PCOS patients undergoing IVF/intracytoplasmic sperm injection (ICSI) using GnRH antagonist protocol with human chorionic gonadotropin trigger between January 2014 to December 2019. **Methods and Material:** Data related to patient's age, body mass index, day 2/3 serum FSH, serum LH, day 2/3 LH/FSH ratio, and infertility treatment-related variables were collected from the patient record files. IVF cycle characteristics, number of oocytes retrieved, number of embryos transferred were also recorded. The clinical pregnancy rate per embryo transfer was calculated. **Statistical Analysis:** Statistical software SPSS IBM version 24.0 was used to analyze the data. Descriptive statistics such as mean, standard deviation , and range values were calculated. To compare the difference between the groups, the paired *t*-test was applied for continuous variables and the Chi-square test for categorical variables. A value of $P < 0.05$ was considered statistically significant. **Results:** High basal day 2/3 LH level and day 2/3 LH/FSH ratio have no statistically significant effect on embryos formed, embryo transferred, and clinical pregnancy rate. However, fertilization rates were significantly less in these groups. **Conclusion:** The elevated basal day 2/3 LH and LH/FSH ratio do not impair the outcome of GnRH antagonist protocol treated IVF/ICSI cycles in PCOS women.

Keywords: *Basal luteinizing hormone, gonadotropin-releasing hormone antagonist, human chorionic gonadotropin trigger, luteinizing hormone/follicle-stimulating hormone, polycystic ovary syndrome*

Introduction

The basal day 2/3 luteinizing hormone (LH) and LH/follicle-stimulating hormone (LH/FSH) ratio are

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notably hoisted in polycystic ovary syndrome (PCOS) patients.[1] Its latent detrimental influence on human reproduction is the subject of debate.[2-4] Prompted by these findings, we attempted to examine whether high basal day 2/3 serum LH levels and day 2/3 LH/FSH ratio affects *in vitro* fertilization (IVF) cycle outcome in PCOS patients undergoing controlled ovarian hyperstimulation using gonadotropin-releasing hormone (GnRH) antagonists. These findings may help to clarify whether the presence of high basal LH necessitates the need to be suppressed before commencing IVF.

Subject and Methods

A retrospective cohort study was conducted in Assisted Reproductive Technique Center, Department of Obstetrics and Gynaecology, at a tertiary care institute, on PCOS patients undergoing IVF/intracytoplasmic sperm injection (ICSI) between January 2014 and December 2019. The approval was obtained from the Institute Ethics Committee. All participants provided written informed consent before undergoing ART cycles and all the data included in the analysis were anonymized.

PCOS was defined according to the Rotterdam criteria:[5] (i) oligo- or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism, and (iii) polycystic ovaries on ultrasound. Two out of three criteria were required for the diagnosis of PCOS after excluding all other endocrine pathologies. All the patients who fulfilled the eligibility criteria during the study period were included for analysis. Data related to patient's age, body mass index, day 2/3 serum FSH, serum LH, day 2/3 LH/FSH ratio, and infertility treatment-related variables were collected from the patient record files. IVF cycle characteristics, number of oocytes retrieved, and number of embryos transferred were also recorded.

Inclusion criteria

The antagonist protocol cycles with PCOS or PCOS + TUBAL or PCOS + Male (Donor semen IVF) as factors of infertility were included. Only fresh transfers were included in this study. No pre-treatment like oral contraceptives was given to patients before enrolment.

Exclusion criteria

The cycles with agonist or dual triggers were excluded from the study groups. GnRH-agonist triggering is associated with the increased rate of mature oocytes retrieved in normal and high responders,[6,7] thus only human chorionic gonadotropin (hCG) trigger cycles were included to remove this bias. Frozen thawed embryo transfer (FET) cycles were not taken into account.

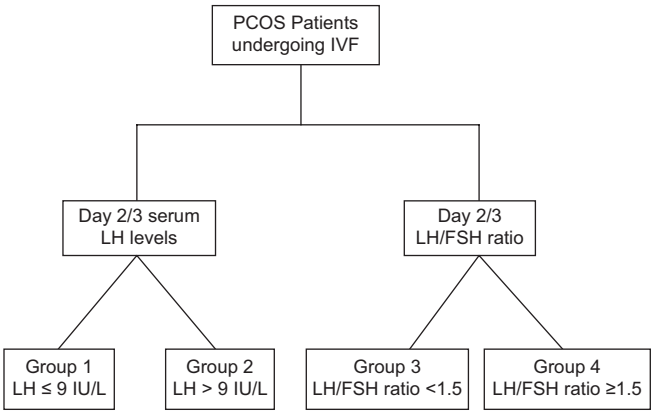
Methodology

The IVF cycles were classified into two groups according to Day 2/3 serum LH levels, namely Group 1 (LH ≤9 IU/L) and Group 2 (LH >9 IU/L). Another two groups were categorized according to Day 2/3 LH/FSH ratio viz. Group 3 (LH/FSH ratio <1.5), and Group 4 (LH/FSH ratio ≥1.5), respectively [Flow Chart 1].

Due to the small number of patients, the LH/FSH ratio was defined according to the previous study by Wiser *et al*.[8] The cut off value for basal LH levels is also based on the conclusions drawn from another study which correlated LH concentrations with ovulation and conception.[9]

Recombinant FSH (Gonal F, Merck, Serono SA, Italy) was started from Day 2 of cycle during flexible antagonist protocol, the starting dose of which was individualized as per patient characteristics. The GnRH antagonist, Cetrorelix acetate (Cetrotide; Merck Serono, Italy) 0.25 mg/day was started when the diameter of the lead follicle was 14 mm. Follicle monitoring was done according to the ovarian response. Recombinant hCG (Ovitrelle, Merck Serono SA, Italy) 250 μg was administered when 2–3 follicles achieved 17–18 mm diameter and oocyte retrieval was performed after 34–36 h. Up to 3 embryos were transferred on day 2/3 or 5 depending on the embryo quality. A serum ß-hCG was checked 14 days after ET and USG for clinical pregnancy was done 2 weeks after positive hCG test.

ICSI was performed in elderly patients with previous IVF failures, whereas IVF was done in all other cases. No FET cycles were included in the analysis. The clinical characteristics, embryological data, and pregnancy outcomes were compared between Group 1 and 2 and Group 3 and 4. The clinical pregnancy is defined as a viable pregnancy when there is evidence of a gestational sac, embryo and fetal heart rate at the time of ultrasonographic evaluation. Clinical pregnancy



Flow Chart 1: Methodology

rate, being more relevant, is calculated as the number of clinical pregnancies per ET. Fertilization rate is the total number of embryos formed divided by the total number of oocytes inseminated or injected.

Statistical analysis

Data were computerized using an MS office Excel Spreadsheet, and analysis was carried out using statistical software IBM SPSS Statistics for Windows Version 24.0 (IBM Corp. Armonk, NY, USA). Descriptive statistics such as mean, standard deviation, and range values were calculated. The study was powered enough for the primary objective. To compare the difference between the groups, the paired *t*-test was applied for continuous variables and the Chi-square test for categorical variables. A value of $P < 0.05$ was considered significant.

Results

Nine hundred and sixty-two IVF/ICSI cycles were performed during the study period. 235 patients with PCOS as the factor of infertility underwent IVF, of which a total of 164 IVF cycles were evaluated as per inclusion criteria. Out of 164 patients, 148 underwent IVF while 16 had ICSI. All study patients received hCG trigger. 17 patients had agonist triggers and 54 patients underwent dual triggers during the study period and were excluded from the study.

Mild ovarian hyperstimulation syndrome (OHSS) developed in 11 study patients, in whom freeze all approach was used. No patient developed moderate to severe OHSS. The number of patients who underwent fresh ET were 117 out of 164. Freeze all was done in total of 37 patients who had either developed mild OHSS or were at high risk of developing OHSS, as well as in patients with raised serum progesterone on the day of trigger. Failed fertilization occurred in 6 patients. Empty follicle syndrome occurred in four patients.

One hundred and thirty-one patients had day 2/3 serum LH levels ≤9 IU/L (Group 1), and 33 patients had their LH levels >9 IU/L (Group 2). Group 2 patients had significantly higher anti-Müllerian hormone (AMH) levels as compared to Group 1 (10.1 ± 6.3 vs. 7.7 ± 4.7, $P = 0.016$). Serum estradiol levels did not differ significantly but progesterone levels on the day of the trigger were significantly higher in Group 2 (3.05 ± 4.9 vs. 1.6 ± 1.9, $P = 0.007$). The number of fresh ETs was also significantly higher in Group 1 as compared to Group 2 ($P < 0.05$).

The fertilisation rate of oocytes was significantly higher in Group 1 as compared to Group 2 (62% ± 28% vs. 51.1% ± 35.5%, $P = 0.02$). But there was no statistically significant difference between the total number of embryos formed, embryo transferred, implantation rate, and clinical pregnancy rate between both the groups [Table 1].

On evaluating IVF cycles according to LH/FSH ratio, 124 patients had day 2/3 LH/FSH ratio <1.5 (Group 3), and 40 patients had ≥1.5 LH/FSH ratio (Group 4) [Table 2]. Group 4 had significantly higher antral follicle count (AFC) and AMH as compared to Group 3 (25.4 ± 9.3 vs. 20.2 ± 8.3, $P = 0.001$ and 10.3 ± 6.4 ng/ml vs. 7.5 ± 4.4 ng/ml, $P = 0.002$). The endometrial thickness on the day of the trigger did not differ significantly between the two groups. On comparing the total dose of gonadotropins used and total days of stimulation, it was found that Group 4 required significantly lesser dose of gonadotropins and lesser days of stimulation (9.9 ± 1.1 days) as compared to 10.4 ± 1.5 days for Group 3 ($P = 0.04$). Progesterone levels on the day of the trigger were significantly higher in Group 4 as compared to Group 3 (3.2 ± 4.7 ng/ml vs. 1.5 ± 1.8 ng/ml with $P = 0.001$). The fertilization rate of oocytes was significantly higher in Group 3 as compared to Group 4; however, the implantation rate and clinical pregnancy rate were not significantly different between the groups ($P > 0.05$).

Discussion

PCOS is a common reproductive endocrine disorder frequently associated with elevated endogenous LH secretion, menstrual cycle abnormalities, infertility, and high rates of spontaneous abortion, illustrating the likely unpredictable effects of LH. Undue raised LH appears to have adverse effects on the pregnancy outcome.[10-13] Escalated production of androgens associated with high LH concentrations, along with their ineffectual aromatization to estrogens related to the low FSH levels in PCOS patients, leads to local androgen surplus and estrogen shortfall within the ovary.[14] It accounts for a potent androgenic domain for the follicle which halts the follicular growth. This results in chronic anovulation in patients with PCOS, which forms the basis for the cause of infertility.[10]

GnRH agonist long protocols were the standard and most commonly used protocols for COS during IVF.[15] However, OHSS following hCG administration in PCOS is a known safety concern. To curb this hurdle, GnRH antagonist protocols with the use of GnRH agonist triggering emanates.[16] The GnRH antagonist has thus presented the IVF-ET a patient-friendly and safe procedure with high efficacy.[17]

In the present study, patients with PCOS, who underwent flexible GnRH antagonist protocol with hCG

Table 1: Controlled ovarian hyperstimulation characteristics according to basal luteinizing hormone levels

Parameters	Mean±SD		*P*
	Group 1 (*n*=131)	Group 2 (*n*=33)	
Age (years)	30.4±3.5	31.1±4.2	0.34
BMI (kg/m^2)	25.3±3.8	24.8±2.9	0.56
AFCs	20.8±8.6	24.1±9.5	0.052
AMH (ng/ml)	7.7±4.7	10.1±6.3	0.016
Endometrial thickness (mm) on day of trigger	8.4±1.6	7.9±1.0	0.14
Total dose of rec-FSH (IU)	2269.9±759.0	2087±796.3	0.14
Total days of stimulation (days)	10.3±1.5	10.1±1.1	0.43
Estradiol (on day of trigger) (pg/ml)	4660.9±5742.5	3582.3±1704.6	0.28
Progesterone (on day of trigger) (ng/ml)	1.6±1.9	3.05±4.9	0.007
Total number of oocytes retrieved	11.5±6.2	10.03±9.1	0.263
Fertilization rate (%)	62±28	48±35	0.02
Total number embryos formed	7.1±4.2	5.9±6.2	0.20
Total number of embryos transferred	2.4±1.2	1.8±1.4	0.06
Number of embryo transfers (*n*)	100	17	0.03
Implantation rate (%)	12	6.8	0.45
Clinical pregnancy rate (%)	19.5	17.4	1.0

BMI=Body mass index, SD=Standard deviation, FSH=Follicle-stimulating hormone, AFCs=Antral follicle counts, AMH=Anti-müllerian hormone

Table 2: Controlled ovarian hyperstimulation characteristics according to luteinizing hormone/follicle-stimulating hormone levels

Parameters	Mean±SD		*P*
	Group 3 (*n*=124)	Group 4 (*n*=40)	
Age (years)	30.4±3.6	30.9±3.6	0.45
BMI (kg/m^2)	25.3±3.8	24.9±3.0	0.53
AFC	20.2±8.3	25.4±9.3	0.001
AMH (ng/ml)	7.5±4.4	10.3±6.4	0.002
Endometrial thickness (mm) on day of trigger	9.1±1.47	8.6±1.4	0.06
Total dose of rec-FSH (IU)	2342±786.9	1895±596.4	0.001
Total days of stimulation (days)	10.4±1.5	9.9±1.1	0.04
Estradiol (on day of trigger) (pg/ml)	4649±5867.3	3805.9±1991.2	0.37
Progesterone (on day of trigger) (ng/ml)	1.5±1.8	3.2±4.7	0.001
Total number of oocytes retrieved	11.3±5.9	10.8±9.3	0.67
Fertilization rate (%)	63.3±25.8	51.1±35.5	0.02
Total number embryos formed	6.9±4.1	6.4±6.3	0.54
Total number of embryos transferred	2.1±1.3	1.6±1.5	0.03
Number of embryo transfers (*n*)	97	20	0.04
Implantation rate (%)	10.2	6.9	0.50
Clinical pregnancy rate	21.5	17.1	0.29

BMI=Body mass index, SD=Standard deviation, FSH=Follicle-stimulating hormone, AFC=Antral follicle count, AMH=Anti-müllerian hormone

trigger were included. They were categorized based on basal LH and LH/FSH ratio. Homburg *et al*.[9] observed basal LH concentrations in PCOS women significantly lower in those who conceived (12.4 IU/l) than in those who did not (19 IU/l) and in those whose pregnancy progressed (9.6 IU/l) than in those with the early loss of pregnancy (17.9 IU/l). Regan *et al*. investigated the relation between prepregnancy follicular-phase serum LH concentrations and outcome of pregnancy prospectively in 193 women with regular spontaneous menstrual cycles using basal LH 10 IU/l as cut-off value.[18] Considering the small sample size of the present study, number of patients with basal LH >10 IU/l were relatively less, hence 9 IU/l was chosen to be the cut-off for this study.

Only a few studies have evaluated the significance of the subgroup with high LH/FSH ratio. The cut-off value for high LH/FSH ratio is not yet defined. Studies have considered the LH/FSH ratio of 2 or 3.[19,20] However, LH/FSH ratio of >1.5 was considered

significant in *in-vitro* maturation (IVM) treatment.[8] Therefore we have taken cut-off value of LH/FSH ratio of >1.5.

The starting dose of recombinant FSH was individualized as per the patient characteristics. Several studies have pointed that the reduced dosages of FSH alleviate the ovarian response. The efficacy is not compromised and instead, the safety profile is improved in terms of OHSS prevention.[21,22]

It has been observed in our study that high basal day 2/3 LH level and LH/FSH ratio have no statistically significant effect on the number of oocytes retrieved, embryos formed, and clinical pregnancy rate. Ganor-Paz *et al*. also concluded that high LH/FSH ratio >1.5 had no adverse effect on pregnancy rates in PCOS women undergoing IVF with GnRH agonist/antagonist protocols or IVM treatments.[23]

Geng *et al*. evaluated the impact of basal serum LH and LH/FSH ratio on the clinical outcomes of 134 *in vitro* fertilisation-ET in patients with PCOS in a retrospective analysis. The clinical characteristics, embryological data, and pregnancy outcomes were compared and analyzed between the groups. They observed that the high basal LH level or a high LH/FSH ratio did not produce an evident detrimental effect on the clinical outcomes of IVF-ET in women with PCOS, which was also observed in our study. However, in their study, the patients were administered oral contraceptives for pretreatment before long GnRH-agonist protocol.[24] On the contrary, Stanger and Yovich reported that IVF had a significantly lower success rate in patients with an elevated basal serum LH level.[25]

Fertilization rate is significantly higher in Group 1 and Group 3 with LH <9 IU/L and LH/FSH ratio <1.5 respectively, which may be due to nonsignificantly higher number of oocytes retrieved in these groups. However, the increased fertilization rate failed to show any significant difference in the clinical pregnancy rate. In contrast, Orvieto *et al*. did not find any difference between the groups regarding the fertilization rate.[19] Our study results did not exhibit any difference between the total number of oocytes retrieved and clinical pregnancy rate between the groups with LH/FSH ratio ≥1.5 or LH/FSH <1.5 which was similar to the findings of Orvieto *et al*.[19] They evaluated 151 IVF cycles and concluded that grouping patients according to their basal day-3 LH/FSH ratio (<2 and ≥2) did not divulge any significant difference in the clinical outcome of the IVF cycles.[19]

The number of oocytes retrieved and mean estradiol levels on the day of the trigger are less in groups with high basal LH and LH/FSH ratio although statistically insignificant. The increased production of androgens by the relatively high LH concentrations coupled with the inefficient aromatization to estrogens caused by the relatively low FSH concentrations in PCOS patients result in local androgen surplus and paucity of estrogen within the ovary.[14] Hence, the higher baseline LH/FSH ratio leads to greater impairment of follicular development. Tesarik and Mendoza showed that the addition of 17 β Estradiol (E2) to oocyte maturation medium did not produce any obvious effects on either germinal vesicle (GV) breakdown or further meiotic progression, but it improved the fertilization and cleavage rates of *in vitro* matured (IVM) oocytes. E2 can consequently impact the quality of maturing oocytes, further fertilization potential, and early postfertilization development.[26] The same authors later suggested that androgens can induce unfavorable effects on the oocyte developmental potential by offsetting the nongenomic, Ca2+-mediated action of estrogens on GV-stage oocytes.[27] The number of follicles developed, and oocytes retrieved were also found to be inversely associated with the baseline LH/FSH ratio in PCOS patients in another study by Tarlatzis *et al*.[20]

High basal LH levels lead to impaired granulosa cell proliferation. Progesterone produced by the granulosa cells diffuses into the theca cells where it is hydroxylated, or this progesterone may acquire access to the circulation if produced in excess amounts, which amounts to high circulating progesterone levels in such patients[28] as observed in Group 2 and 4 in the present study. Friis Wang *et al*. suggested that the late follicular progesterone (P4) level (on the day of trigger) reflects the LH sensitivity of the follicle. Thus, women with high P4 levels on the day of the trigger will be the women who respond maximum to the ovulatory trigger afterward in terms of P4 production and will therefore have the highest P4 level during the early luteal phase leading to advanced endometrium.[29]

There was significantly higher AFC, AMH, lesser doses of gonadotropins used, and lesser days of stimulation required in Group 4 with LH/FSH ratio ≥1.5. This is in accordance with the study done by Geng *et al*.[24] and Biasoni *et al*.[30] This can be attributed to increased ovarian sensitivity index owing to high AMH and thus reducing doses of gonadotropins and days of stimulation.

Thomas *et al*. also concluded that the follicular phase LH concentrations do not forecast IVF fertilization rates or clinical outcomes. When analyzed for serum LH concentrations above the 75th or 95th centile for ≥3 days of an IVF treatment cycle in their study, they observed no difference in pregnancy rates, fertilisation rates, the median number of oocytes fertilised or retrieved.[31]

However, in a survey by Tarlatzis *et al*. on PCOS patients stimulated with HMG or buserelin-long/HMG, they summarise that the raised basal LH/FSH had an adverse effect on the number of follicles and oocytes, as well as on oocyte maturation. Furthermore, they observed that suppressing LH by the use of GnRH agonists in the long protocol reversed this detrimental effect on follicle and oocyte development.[20]

Limitations of the study

The foremost limitations of this study are its retrospective nature and small sample size. Furthermore, in the analyzed cohort, very few patients had very high LH levels. However, this does not make much difference as in the clinical practice; also, we seldom see patients with exceptionally high LH levels. The exclusion of women who had an agonist/dual trigger (and are likely to be those with a higher response) might have affected the results.

Conclusion

The elevated basal day 2/3 LH and LH/FSH ratio do not impair the outcome of GnRH antagonist protocol treated IVF/ICSI cycles in PCOS women. Therefore, suppressing LH values before IVF is not clinically worth in individual patient management. The role of raised LH in PCOS seems to be exaggerated without adequate evidence. However, more randomized prospective studies are needed to endorse these findings.

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Conflicts of interest

There are no conflicts of interest.

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