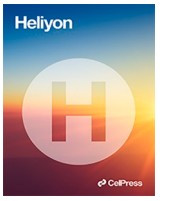
Heliyon 9 (2023) e16233

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Hypersecretion of basal luteinizing hormone and an increased risk of pregnancy loss among women with polycystic ovary syndrome undergoing controlled ovarian stimulation and intrauterine insemination

Bin Wang, Zhiling Li *

Reproductive Center, The First Affiliated Hospital of Shantou University Medical College, Shantou University, Shantou, Guangdong, People's Republic of China

ARTICLE INFO

Keywords:
Live birth
IUI
LH
Miscarriage
PCOS
Pregnancy

ABSTRACT

Introduction: The relationship between basal luteinizing hormone (LH) and reproductive outcomes in women with polycystic ovary syndrome (PCOS) undergoing intrauterine insemination (IUI) has remained largely unknown, warranting further investigations. Accordingly, this study aimed to investigate the possible association of basal LH with reproductive outcomes in women with PCOS women undergoing IUI to gain a better understanding of this topic.

Material and methods: Data from 533 cycles of controlled ovarian stimulation (COS) and IUI treatments from PCOS women were retrospectively analyzed. Statistical methods, including univariate analysis, receiver operating characteristic (ROC) curve, quartile division, and Spearman rank correlation analysis, were utilized.

Results: Basal LH resulted as the most significant contributor to pregnancy ($P < 0.001$). ROC analysis revealed that the predictive power of basal LH on pregnancy was stronger compared to other factors (areas under the curve 0.614, 95% CI 0.558–0.670, $P = 0.000$). Analysis based on quartile division unveiled a stair-shaped relation of basal LH with pregnancy or live birth as well as a positive linear relation between basal LH and early miscarriage (all P trend<0.05). Basal LH of 11.69 mIU/ml was the point above which early miscarriage grew significantly while pregnancies and live births ceased to increase. Moreover, basal LH was positively correlated with antral follicle count (AFC), number of mature follicles on the trigger day, clinical pregnancy, live birth, and multiple pregnancies (all $P < 0.05$). The number of mature follicles on the trigger day was positively correlated with clinical pregnancy, early miscarriage, and multiple pregnancies (all $P < 0.05$). AFC was positively correlated with clinical pregnancy ($P < 0.05$).

Conclusion: Hypersecretion of basal LH was associated with an increased risk of pregnancy loss among PCOS women undergoing COS and IUI. Basal LH may have predictive value on pregnancy achievement in women with PCOS undergoing COS and IUI.

* Corresponding author. Reproductive Center, The First Affiliated Hospital of Shantou University Medical college, Shantou University, Shantou, 515041, Guangdong Province, People's Republic of China.
E-mail address: stlizhiling@126.com (Z. Li).

https://doi.org/10.1016/j.heliyon.2023.e16233
Received 21 December 2022; Received in revised form 9 May 2023; Accepted 10 May 2023
Available online 13 May 2023

1. Introduction

Polycystic ovary syndrome (PCOS) is currently the most common endocrine disease among women of reproductive age, affecting 20% of infertile women [1,2]. On ultrasound examination, PCOS is clinically characterized by oligo-anovulation, hyperandrogenism, and polycystic ovaries [3]. However, there is still no effective therapy for PCOS, and currently used strategies mainly focus on relieving symptoms and adopting a healthy lifestyle to minimize the possibility of complications [4]. Women with PCOS encounter difficulties in conceiving offspring due to oligo-anovulation [5]. Fortunately, controlled ovarian stimulation (COS) may help women with PCOS to get over this barrier and restore ovulation [6,7].

Intrauterine insemination (IUI) is a widely-used technique in assisted reproduction. This approach is commonly adopted before proceeding to complicated method of in vitro fertilization (IVF) and embryo transfer, as it can improve the chance of pregnancy whilst being easy and simple to perform, less invasive and relatively low-cost [8]. COS and IUI are now considered the first-line treatment for infertile couples with PCOS [9].

Luteinizing hormone (LH), a glycoprotein secreted by the pituitary gland, is thought to have a critical role in the follicle's steroidogenesis, growth, and final maturation [10]. However, the optimal level of LH during ovarian stimulation remains unclear [11]. Furthermore, although most PCOS women are featured by hypersecretion of basal LH, basal LH within the normal range may also be found in a small proportion of PCOS women due to disease heterogeneity [12]. Hence, the diagnostic value of basal LH on PCOS remains controversial [13].

Previous studies have shown that basal LH is associated with reproductive outcomes in PCOS women; however, reported findings are somewhat inconsistent [14–19]. Moreover, all previous studies were conducted in the context of IVF [14–19], leaving the association between basal LH and reproductive outcomes in women with PCOS undergoing IUI largely unknown and warranting further investigations. Consensus in reproductive medicine recommends at least three cycles of IUI for infertile PCOS women before switching to IVF [20]. A previous retrospective study also showed that the cumulative clinical pregnancy rate per patient might reach 38.59% after 3 cycles of IUI [20]. Therefore, studying influencing factors on reproductive outcomes in women with PCOS undergoing IUI is necessary.

In the present study, we retrospectively investigated the possible association of basal LH with reproductive outcomes in PCOS women who underwent COS and IUI in the present center. To our knowledge, this is the first report of this kind, and it will hopefully provide more information to better understand the association of basal LH with reproductive outcomes of PCOS women undergoing IUI.

2. Material and Methods

2.1. Study subjects

Our study registered information from PCOS couples who received COS and IUI therapies at the Reproductive Center of The First Affiliated Hospital of Shantou University Medical College between January 1, 2016 and December 31, 2020. Demographic and clinical data were acquired through the electronic medical record. PCOS was diagnosed as per the Rotterdam Criteria [3]. The excluding criteria were the following: spousal sperm abnormality, women with body mass index (BMI) greater than 30 kg/m^2, endometriosis, blockage of the oviduct and anomaly of uterus or pelvic cavity. As shown in Fig. 1, 533 cycles of COS and IUI therapies were eventually included. Prior to initiation of COS and IUI, each couple received a routine infertility checkup in the Reproductive Center. For men, semen quality was assessed after 3–5 days of abstinence; for women, the basal hormone levels were tested on day 3–5 of the menstruation.

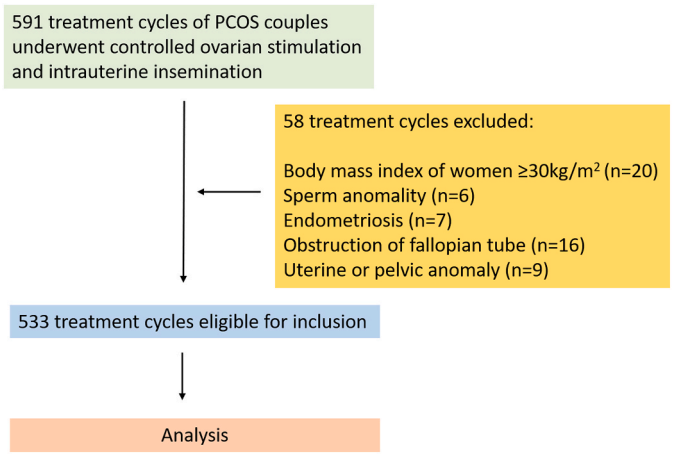


Fig. 1. Flowchart illustrating subject selection. PCOS, polycystic ovary syndrome.

Our study was authorized by The Institutional Ethics Committee of our hospital (Authorization ID: 2015). All participants provided written informed consent. This study was conducted according to the principles of the Declaration of Helsinki.

2.2. COS and IUI protocols

The starting dose of ovarian stimulation was tailored by the fertility doctor after completely evaluating patients' age, BMI, current ovarian reserve, and previous history of ovarian response. Ovarian stimulation was initiated 3–5 days after the menstrual cycle.

For ovarian stimulation utilizing human menopausal gonadotropin (HMG), stimulation was carried out as depicted in our previous study [21]. Similarly, for ovarian stimulation using clomiphene or letrozole, stimulation was performed as stated in our previous study [21].

Ovulation were induced either with 10,000 IU HCG (Livzon, China) or 0.25 mg rHCG (Merck Serono, Switzerland) or 0.1–0.2 mg GnRH-a (IPSEN PHARMA, France) plus 6000 IU HCG when at least one dominant follicle with a diameter of $\geq$18 mm had emerged. IUI was performed 24–36 h after the ovulation induction, with the help of a sterile catheter. Women were then advised to have bedrest for 30 min after the operation. Serum βeta-human chorionic gonadotropin (β-hCG) was measured 14 days after the IUI operation to ascertain the existence of pregnancy.

Beginning from the day after IUI, luteal support was given individually in the form of 10 mg Dydrogesterone (Abbott Laboratories, USA) 2 or 3 times each day for 15–16 days, with the supplement of 2000 IU hCG every three days when necessary. If a live intrauterine sac was confirmed, the luteal support was kept for 10-12 additional weeks.

Five or six weeks after the IUI operation, a transvaginal ultrasound scan was additionally conducted to detect clinical pregnancy; clinical pregnancy was documented if an intrauterine sac was present. Loss of a pregnancy during the first 12 weeks was considered as early miscarriage. Live birth was defined as the birth of a live born infant with a gestational age of **>** 28 weeks.

2.3. Determination of hormonal concentration

Concentration of hormone was determined using the method of chemiluminescence (Abbott Biologicals B·V., Weesp, Netherlands) with reference to producer's manual in the Department of Clinical Laboratory. Both inter-assay and intra-assay coefficients of variation were under 10% for all measurements.

2.4. Analysis of semen quality

Analysis of semen quality was performed in accordance to the World Health Organization Criteria in the Andrology Laboratory of our center. Two or 3 h before the prearranged time of insemination, semen samples were obtained by masturbation after 3–5 days of abstinence. Semen samples were then prepared using the density gradient centrifugation method as described in previous study [22].

2.5. Follow-up interviews

Follow-up interviews started 2 weeks after the IUI operation and every other month after that. Senior nurses collected information concerning health condition and pregnancy via telephone calls. Follow-up interviews were cancelled if one of the below mentioned conditions happened: (1) no positivity of serum β-hCG 14 days after IUI; (2) early miscarriage; (3) birth of a viable infant. The follow-up rate of the current study was 100%.

2.6. Statistical analysis

Statistical analysis was conducted using the Statistic Package for Social Science 20.0 for Windows (SPSS 20.0, IBM, NY, USA). For continuous data, Kolmogorov-Smirnov normality test was first employed to ascertain the distribution. According to the type of distribution, continuous data were expressed as mean $\pm$ standard deviation or median (25th-75th percentiles). Normally distributed continuous data were analyzed with the T-test, and abnormally distributed continuous data were analyzed with the Mann-Whitney *U* test. For data with abnormal distribution, the Kruskal-Wallis H test was utilized to conduct multiple comparisons. Categorical data were shown as number or percentage. Categorical data were analyzed using Pearson's Chi-square or Fisher's exact tests. The receiver operating characteristic (ROC) curve was employed to elucidate the predictive value of specific factors on the achievement of clinical pregnancy. In ROC analysis, the occurrence of pregnancy (categorical variable, yes = 1, no = 0) was defined as the dependent variable, while bLH, bFSH, bLH/FSH ratio, AFC, and number of mature follicles of the trigger day were incorporated as the independent variables. Next, ROC analysis was conducted in the SPSS using the default settings. The value of AUC (area under the curve) reflects the predictive power of any specific factor on the occurrence of pregnancy. The AUC value was statistically significant only when the corresponding P value < 0.05. Quartile division was used to assist analysis of the relation between basal LH level and major indicators of reproductive outcomes. Data were first arranged in ascending order by basal LH concentration and then divided into 4 quartiles, with the 25th, the 50th, and the 75th percentile of basal LH concentration as the three dividing points. Additional analysis was then carried out on this basis. Spearman rank correlation analysis was conducted to investigate the correlation between two factors. Missing data were addressed using the listwise deletion method as suggested by SPSS. A two-tailed P value of <0.05 was regarded as statistically significant. The power of all the tests used in this study was $>80\%$, as calculated by NCSS-PASS (NCSS Inc., USA, 2005 version).

3. Results

3.1. Basal LH, basal FSH, basal LH/FSH ratio, antral follicle count, and number of mature follicles of the trigger day as factors contributing to pregnancy

Univariate analysis was first used to screen clinical factors associated with pregnancy in PCOS women. As shown in Table 1, antral follicle count, basal LH, basal FSH, basal LH/FSH ratio, and the number of mature follicles on the trigger day were all factors contributing to pregnancy in women with PCOS, with basal LH being the most significant one ($P < 0.001$). Accordingly, in our further analyses, we mainly focused on the relation of basal LH with the reproductive outcomes in PCOS women.

3.2. Predictive value of basal LH, basal FSH, basal LH/FSH ratio, antral follicle count, and number of mature follicles on the trigger day of pregnancy

ROC curve was employed to elucidate the predictive value of basal LH, basal FSH, basal LH/FSH ratio, antral follicle count and the number of mature follicles on the trigger day on achievement of clinical pregnancy in PCOS women. As illustrated in Fig. 2A, the predictive power of basal LH was stronger when compared to other factors (areas under the ROC curve [AUC] 0.614, 95% confidence interval 0.558–0.670, for basal LH, $P = 0.000$). Further analysis revealed that the cut-off value of basal LH was 7.57 mIU/ml.

Next, we combined all the significant markers to produce a new ROC curve. Data from statistical analysis showed that AUC for the new curve was slightly improved when compared to any of the five individual markers abovementioned (0.650 vs. 0.556, 0.614, 0.590, 0.569, and 0.568, Fig. 2B).

3.3. Concentration-dependent relation of basal LH with clinical pregnancy, early miscarriage, multiple pregnancies, antral follicle count, and number of mature follicles on the trigger day

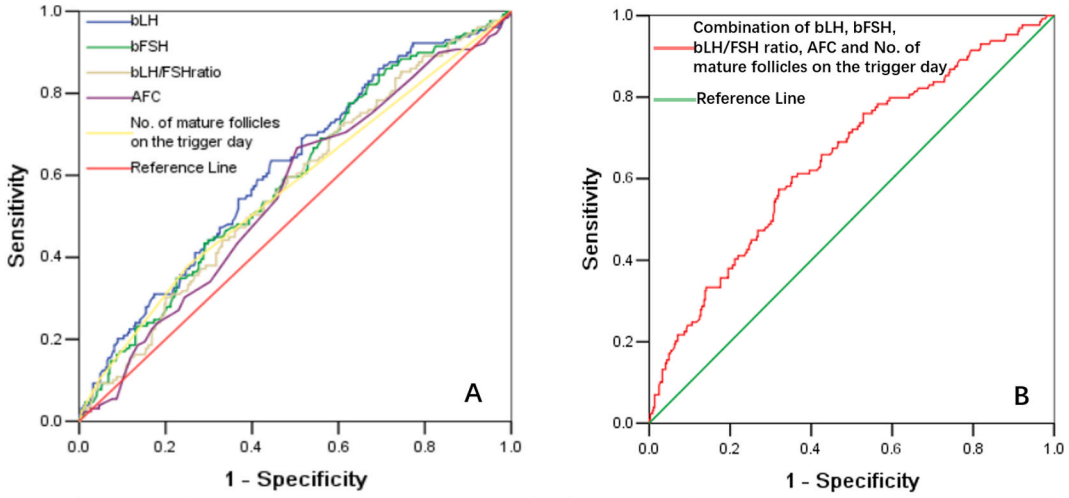
Based on quartile division, we subsequently analyzed the relation of basal LH level with major indicators of reproductive outcomes in PCOS women. As indicated in Table 2 and Fig. 3A, as basal LH level increased (from <4.54 mIU/ml in the first quartile to 4.54–7.51 mIU/ml in the second quartile and 7.51–11.69 mIU/ml in the third quartile), clinical pregnancy rates steadily increased as well (from 12.78% of the first quartile to 23.52% of the second quartile and 31.81% of the third quartile, $P < 0.000$). However, the clinical pregnancy rate stabilized and reached a plateau when basal LH level >11.69 mIU/ml, the 75th percentile of basal LH concentration (33.33% of the fourth quartile vs. 31.81% of the third quartile). Accordingly, the relation between basal LH and pregnancy in women with PCOS resembled a stair-shaped curve. A similar stair-shaped relation was also found between basal LH and live birth rate (7.51%, 15.44%, 21.21%, and 21.96% for the first, the second, the third and the fourth quartile, respectively, $P < 0.000$, Table 2 and Fig. 3C). In addition, early miscarriage rates gradually increased as basal LH level rose (3.0%, 3.67%, 4.54%, and 8.33% for the first, the second, the third, and the fourth quartile, respectively, $P = 0.044$, Table 2 and Fig. 3B). Furthermore, the third and the fourth quartiles, with relatively higher basal LHs were associated with elevated multiple pregnancy rates (3.0% of both the third and fourth quartiles vs. 0.75% of the first quartile and 0% of the second quartile, Table 2 and Fig. 3D).

Moreover, we also explored the relation between basal LH level and the number of mature follicles on the trigger day. Starting from the first to the fourth quartile, the number of mature follicles on the trigger day gradually rose as the basal LH level increased ($P < 0.05$, Fig. 3E). Likewise, a similar relation between basal LH and antral follicle count was also noted (see Fig. 3F).

Table 1
Baseline characteristics and reproductive outcomes of pregnant and nonpregnant patients.

Characteristics	Clinical pregnancy (n = 135)[a]	Nonpregnancy (n = 398)[a]	*P* value
Age (years)	28 (20–38)	29 (21–40)	0.194
Duration of infertility (years)	3 (1.0–10)	3 (0.4–9)	0.162
Etiology of infertility			
Primary	99 (73.33%)	296 (74.37%)	0.812
Secondary	36 (26.67%)	102 (25.63%)	
Body mass index (kg/m^2)	21.8 (17.0–28.1)	22.0 (16.9–30.7)	0.216
Antral follicle count	26 (5–55)	24 (5–55)	**0.047**
Basal LH (mIU/ml)	9.13 (1.39–30.80)	6.98 (0.42–29.60)	**0.000**
Basal FSH (mIU/ml)	6.39 (2.9–50.8)	5.91 (0.9–11.8)	**0.001**
Basal LH/FSH ratio	1.604 (0.22–5.21)	1.393 (0.0–5.21)	**0.026**
Basal estradiol (pg/ml)	45 (6–119)	44 (6–405)	0.889
Basal progesterone (ng/ml)	0.355 (0.01–33.00)	0.345 (0.01–2.22)	0.800
Total dosage of gonadotrophin used (IU)	425 (75–2275)	450 (50–3575)	0.755
Endometrium thickness on the trigger day (mm)	10 (4.8–6.0)	10 (5.0–16.5)	0.769
Number of mature follicles on the trigger day	1.467 ± 0.747	1.328 ± 0.636	**0.005**

Abbreviation: LH, luteinizing hormone; FSH, follicle-stimulating hormone. Continuous data are presented as mean ± standard deviation or median (minimum-maximum) depending on distribution. Categorical data are expressed as number (percentage). a: missing data were addressed using the listwise deletion method.



	Panel A					Panel B
	bLH	bFSH	bLH/FSH ratio	AFC	No. of mature follicles on the trigger day	Combination of bLH, bFSH, bLH/FSH ratio, AFC and No. of mature follicles on the trigger day
AUC value	0.614	0.590	0.569	0.556	0.568	0.650
P value	0.000	0.002	0.019	0.048	0.021	0.000

Fig. 2. Receiver operating characteristic curve of antral follicle count, basal luteinizing hormone, basal follicle-stimulating hormone, bLH/FSH ratio, and the number of mature follicles of the trigger day in relation to the achievement of clinical pregnancy. AFC, antral follicle count; bLH, basal luteinizing hormone; bFSH, basal follicle-stimulating hormone; AUC, Areas under the receiver operating characteristic curve.

Table 2
Analysis of reproductive outcomes, antral follicle count and number of mature follicles on the trigger day based on quartile division of basal luteinizing hormone concentration.

Factors investigated	Concentration of basal luteinizing hormone (n = 533)[a]				P value	P trend
	The first quartile	The second quartile	The third quartile	The fourth quartile		
	<4.54 mIU/ml (n = 133)	4.54–7.51 mIU/ml (n = 136)	7.51–11.69 mIU/ml (n = 132)	>11.69 mIU/ml (n = 132)		
Clinical pregnancy rate	17/133 (12.78%)	32/136 (23.52%)	42/132 (31.81%)	44/132 (33.33%)	0.000	0.000
Early miscarriage rate	4/133 (3.0%)	5/136 (3.67%)	6/132 (4.54%)	11/132 (8.33%)	0.183	0.044
Multiple pregnancy rate	1/133 (0.75%)	0/136 (0%)	4/132 (3.03%)	4/132 (3.03%)	0.116	0.048
Live birth rate	10/133 (7.51%)	21/136 (15.44%)	28/132 (21.21%)	29/132 (21.96%)	0.005	0.001
Antral follicle count	23.99 ± 5.52	25.13 ± 6.22	27.30 ± 8.53	28.28 ± 8.48	0.000 [b]	NA
Number of mature follicles on the trigger day	1.270 ± 0.524	1.308 ± 0.683	1.378 ± 0.693	1.462 ± 0.681	0.046 [b]	NA

Values are presented as number (percentage) or mean ± standard deviation. Data were first arranged in ascending order by basal luteinizing hormone concentration, and then divided into four quartiles with the 25th (4.54), the 50th (7.51) and the 75th (11.69) percentile of basal luteinizing hormone concentration as the three dividing points. Analysis was then carried out on this basis.

[a] missing data were addressed using the listwise deletion method.

[b] multiple comparisons were performed with the Kruskal-Wallis test due to abnormal distribution of the data analyzed. NA: not applicable.

3.4. Correlation analysis among basal LH, clinical pregnancy, early miscarriage, multiple pregnancies, antral follicle count, and number of mature follicles of the trigger day

Spearman rank correlation analysis was performed to investigate the relationship of basal LH with antral follicle count, number of mature follicles on the trigger day, clinical pregnancy, early miscarriage, and multiple pregnancies. As shown in Table 3, basal LH was positively correlated with antral follicle count, number of mature follicles on the trigger day, clinical pregnancy, live birth, and multiple pregnancies (the correlation coefficients were 0.209, 0.119, 0.165, 0.118, and 0.094 respectively, all $P < 0.05$). Besides, the number of mature follicles on the trigger day was also positively correlated with clinical pregnancy, early miscarriage, and multiple pregnancies (all $P < 0.05$, see Table 3). Furthermore, besides the positive correlation between basal LH and antral follicle count, there was a positive correlation between antral follicle count and clinical pregnancy (all $P < 0.05$, see Table 3).

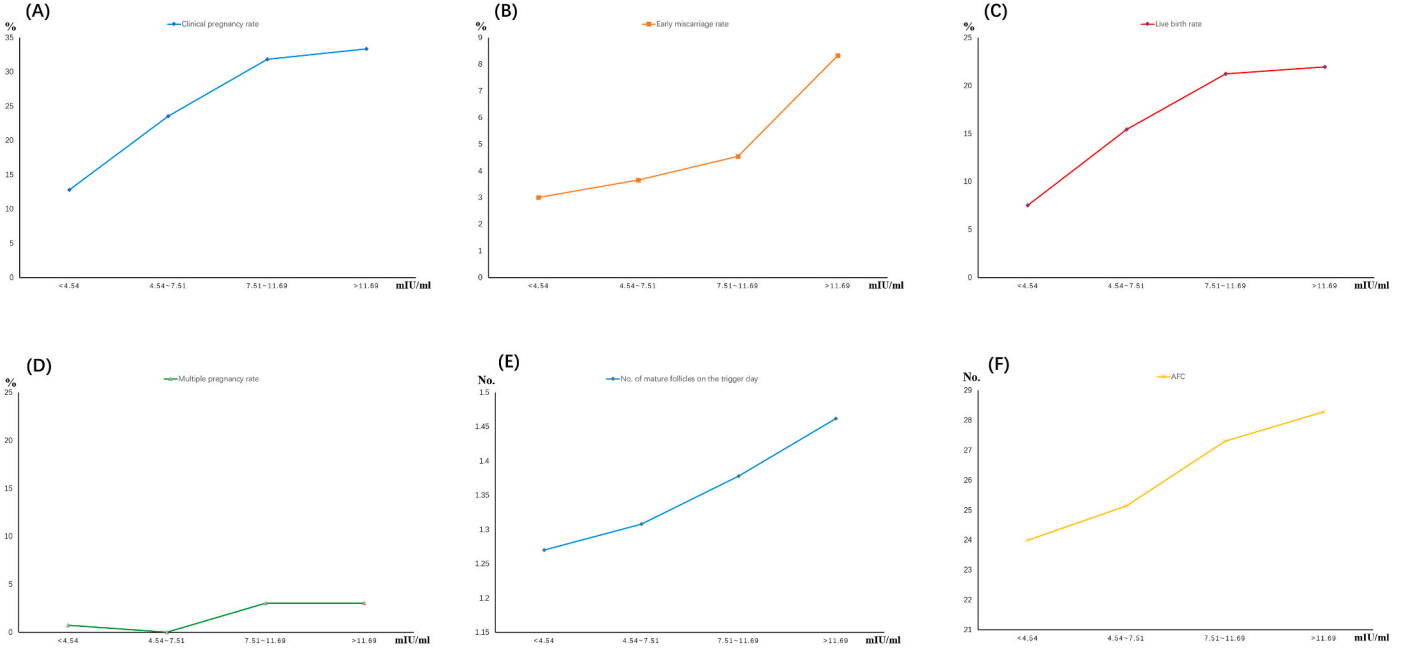


Fig. 3. Change of clinical pregnancy rate, early miscarriage rate, live birth rate, multiple pregnancy rate, antral follicle count (AFC), and number of mature follicles on the trigger day based on quartile division of basal luteinizing hormone concentration. Data were first arranged in ascending order by basal luteinizing hormone concentration and then divided into four quartiles with the 25th (4.54), the 50th (7.51), and the 75th (11.69) percentile of basal luteinizing hormone concentration as the three dividing points. Analysis and drawing were then carried out on this basis.

Table 3
Correlation analysis among basal LH, clinical pregnancy, early miscarriage, live birth, multiple pregnancy, antral follicle count and number of mature follicles of the trigger day (n = 533).

Investigated characteristics[a]		Clinical pregnancy	Early miscarriage	Live birth	Multiple pregnancy	AFC	bLH	Number of mature follicles on the trigger day
Clinical pregnancy	Correlation coefficient	–	0.349**	0.866**	0.225**	0.088*	0.165**	0.121**
	P value	–	0.000	0.000	0.000	0.047	0.000	0.005
Early miscarriage	Correlation coefficient	–	–	−0.118*	0.106*	0.054	0.071	0.090*
	P value	–	–	0.013	0.015	0.222	0.102	0.037
Live birth	Correlation coefficient	–	–	–	0.187**	0.025	0.118*	0.073
	P value	–	–	–	0.000	0.601	0.013	0.127
Multiple pregnancy	Correlation coefficient	–	–	–	–	0.048	0.094*	0.087*
	P value	–	–	–	–	0.283	0.031	0.045
AFC	Correlation coefficient	–	–	–	–	–	0.209**	0.069
	P value	–	–	–	–	–	0.000	0.124
bLH	Correlation coefficient	–	–	–	–	–	–	0.119**
	P value	–	–	–	–	–	–	0.006

Abbreviation: AFC, antral follicle count; bLH, basal luteinizing hormone. *, $P < 0.05$; **, $P < 0.01$. a: missing data were addressed using the listwise deletion method.

4. Discussion

LH is of essential importance in folliculogenesis and ovulation [10]. In addition, hypersecretion of basal serum LH is an essential hallmark of polycystic ovary syndrome (PCOS) [13]. Nevertheless, the prevalence of elevated basal LH or basal LH/FSH ratio can fluctuate between 35% and 77% among PCOS women [12]. As a result, the diagnostic value of basal LH or basal LH/FSH ratio on PCOS remains unclear and debatable [13].

Previous studies have explored the relationship of basal serum LH with the reproductive outcomes in PCOS patients; however, reported findings seem contradictory [14–19]. Moreover, as these previous studies were mainly performed in the context of IVF [14–19], the relationship between basal LH and reproductive outcomes in women with PCOS undergoing controlled ovarian stimulation (COS) and intrauterine insemination (IUI) remains unclear. Compared to IVF, IUI is a simple, less invasive, and low-cost technique [8]. This study focused on the relationship between basal LH and the reproductive outcomes in PCOS women who underwent COS and IUI. To our knowledge, this is the first report of this kind.

First, univariate analysis was used to explore possible contributing factors to pregnancy among PCOS women, finding that basal LH, basal FSH, basal LH/FSH ratio, antral follicle count, and the number of mature follicles on the trigger day were all factors contributing to pregnancy in PCOS women. However, basal LH was the most significant among all the analyzed factors, highlighting the critical role of basal LH in the pregnancy of PCOS women. These findings are consistent with previous studies from IVF settings [11,23].

In addition to basal LH, basal FSH could have clinical significance and is worthy of further study. It has been shown that basal luteinizing hormone concentration is elevated in PCOS while basal FSH remains unchanged or slightly suppressed [24,25]. In the present study, we found that the basal FSH levels in non-pregnant PCOS women were significantly lower compared to pregnant PCOS women. Blank et al. argued that insufficient FSH level contributes to impaired follicular development [26], which may partly explain the findings of the present study. In our future study, we will analyze the effect of basal FSH on reproductive outcomes in PCOS women undergoing COS and IUI.

ROC curve was used to examine the predictive value of the factors above on pregnancy in PCOS women. According to the findings from univariate analysis, the predictive value of basal LH was higher than other factors (AUC of 0.614 for basal LH). However, even though an AUC of 0.614 indicated a relatively low accuracy, it can still be interpreted as reasonable, considering that pregnancy in PCOS women is co-determined by multiple factors, with basal LH just being one of them [5]. Moreover, the cut-off value of basal LH was 7.57 mIU/ml in this study, suggesting that, under the IUI setting, PCOS women with basal LH of 7.57 mIU/ml were most likely to achieve pregnancy. We also combined all the significant markers to produce a new ROC curve. Data from statistical analysis showed that AUC for the new curve was slightly improved when compared to any of the five individual markers (0.650 vs. 0.556, 0.614, 0.590, 0.569, and 0.568, Panel B of Fig. 2), thus suggesting that pregnancy in women with PCOS may also be influenced by other important factors that were not included or analyzed in the current study.

With quartile division, we explored the relation of basal LH with major indicators of reproductive outcomes in women with PCOS, finding a stair-shaped relation between basal LH and pregnancy and a positive linear relation between basal LH and early miscarriage. The stair-shaped relation between basal LH and pregnancy implies that as basal LH level exceeds the third cutting point (11.69 mIU/ml, the 75th percentile of basal LH level), the difficulty in achieving pregnancy considerably increases for PCOS women. Similarly, the positive linear relation between basal LH and early miscarriage revealed that, as basal LH level increases, the possibility of pregnancy loss increases accordingly. Furthermore, as complementary evidence to the previous finding, a stair-shaped relation was also observed between basal LH and live birth, which is a more reliable endpoint for the reproductive outcome. The stair-shaped relation between basal LH and live birth suggested that, as basal LH rises, the difficulty of sustaining the fetus increases, especially when basal LH exceeds the third cutting point (11.69 mIU/ml). Considering the previous findings, we believe that hypersecretion of basal LH may be associated with pregnancy loss.

Moreover, 11.69 mIU/ml, the 75th percentile of basal LH concentration, above which early miscarriage grew significantly while pregnancy and live birth ceased to increase, was close to 10 mIU/ml, a threshold value taken by Regan et al. to define high or low LH group [27]. Regan and colleagues found that serum LH concentration >10 mIU/ml on day 8 of the menstrual cycle was significantly associated with fertility impairment and increased miscarriage among women with regular menstrual cycles [27]. A similar phenomenon was also observed among PCOS women in the present study. Regan et al. even suggested that basal LH might be a powerful predictor of miscarriage, irrespective of obstetric history [27]. A previous study has proposed that high follicular-phase LH levels, rather than the presence of polycystic ovaries, predicted the poor prognosis of fertility among PCOS women [28]. Our results showed that basal serum LH of 11.69 mIU/ml may be used as a reference value by fertility doctors treating PCOS patients who intend to undergo COS and IUI treatments.

Besides, we discovered that the number of mature follicles on the trigger day was positively correlated with clinical pregnancy, early miscarriage, and multiple pregnancies. In addition to the positive correlation of basal LH with antral follicle count (a faithful indicator for ovarian reserve and ovarian responsiveness to drug stimulation [29,30]), there was also a positive correlation between antral follicle count and clinical pregnancy in our study. Accordingly, we believe that PCOS women with a high level of basal LH may have a high ovarian reserve and a high responsiveness to the drug of ovarian stimulation. Hence, it is rational to conclude that PCOS women with high levels of basal LH may yield more mature follicles after undergoing ovarian stimulation compared to those with low levels of basal LH. In turn, more mature follicles may enhance the chance of pregnancy. However, we did not observe an uninhibited pregnancy rise (or live birth) as basal LH increased. Instead, the relation of these two indicators resembled a stair-shaped curve. This seemingly paradoxical discovery implies that more mature follicles associated with high basal LH and high ovarian responsiveness may impair fertilization competence, or the ensuing embryo may have poor survival and be easily aborted.

The mechanism underlying the association between hypersecretion of basal LH and miscarriage remains to be elucidated. Usually,

the preovulatory follicle arrests at the diplotene stage of the first meiotic division and remains dormant, waiting for further stimulus [27]. When LH enters the preovulatory follicle at the midcycle of menstruation, the meiotic division resumes and produces a mature oocyte about 36 h later [27]. It is believed that there is a species-specific time window between the completion of the first meiotic division of the oocyte and its fertilization, during which conditions for fertilization and embryonic development are optimal [31,32]. If the time window is extended by premature exposure to an ovulatory stimulus (LH, for instance), fertilization is impaired and the ensuing embryo has poor survival and is more likely to be aborted [31,32].

We support the hypothesis proposed by Baker et al. [32], suggesting that LH is persistently high throughout the follicular phase in most PCOS women. This hormone may penetrate the follicle and cause the oocyte to mature prematurely, eventually resulting in a physiologically "aged" oocyte. Such oocytes may have impaired fertilization capacity or produce an embryo that implants poorly and is easily aborted [33]. Regardless of the potential mechanism, an elevated level of basal serum LH during the follicular phase leads to an increased risk of pregnancy loss among PCOS women undergoing COS and IUI. Our results suggest that basal serum LH may have predictive value for the achievement of pregnancy among PCOS women undergoing COS and IUI.

There are some shortcomings to our study. Firstly, this was a retrospective study, which should be considered when interpreting our results. Future prospective randomized studies are needed to further verify our results. Secondly, our study was conducted in a single center and had a relatively small sample size. Therefore, reported findings should be further validated by a multi-center clinical trial with sufficient samples in the future.

5. Conclusion

Hypersecretion of basal LH was associated with an increased risk of pregnancy loss among PCOS women undergoing COS and IUI. Basal LH may have predictive value on pregnancy achievement in women with PCOS undergoing COS and IUI.

Funding

This work was supported by Guangdong Science and Technology Department (No. 2016A020218015).

Author contribution statement

Bin Wang: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Zhiling Li: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] D. Garg, R. Tal, The role of AMH in the pathophysiology of polycystic ovarian syndrome, Reprod. Biomed. Online 33 (2016) 15–28.
[2] R.S. Legro, R.G. Brzyski, M.P. Diamond, C. Coutifaris, W.D. Schlaff, P. Casson, G.M. Christman, H. Huang, Q. Yan, R. Alvero, D.J. Haisenleder, K.T. Barnhart, G. W. Bates, R. Usadi, S. Lucidi, V. Baker, J.C. Trussell, S.A. Krawetz, P. Snyder, D. Ohl, N. Santoro, E. Eisenberg, H. Zhang, N.R.M. Network, Letrozole versus clomiphene for infertility in the polycystic ovary syndrome, N. Engl. J. Med. 371 (2014) 119–129.
[3] Rotterdam Eshre Asrm-Sponsored Pcos Consensus Workshop Group, Rotterdam, Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, Fertil. Steril. 81 (2004) 19–25.
[4] H.J. Teede, M.L. Misso, J.A. Boyle, R.M. Garad, V. McAllister, L. Downes, M. Gibson, R.J. Hart, L. Rombauts, L. Moran, A. Dokras, J. Laven, T. Piltonen, R. J. Rodgers, M. Thondan, M.F. Costello, R.J. Norman, P.N. International, Translation and implementation of the Australian-led PCOS guideline: clinical summary and translation resources from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome, Med. J. Aust. 209 (2018) S3–S8.
[5] A.E. Joham, R.J. Norman, E. Stener-Victorin, R.S. Legro, S. Franks, L.J. Moran, J. Boyle, H.J. Teede, Polycystic ovary syndrome, Lancet Diabetes Endocrinol. 10 (2022) 668–680.
[6] T.T. Nguyen, H.T. Doan, L.H. Quan, N.M. Lam, Effect of letrozole for ovulation induction combined with intrauterine insemination on women with polycystic ovary syndrome, Gynecol. Endocrinol. 36 (2020) 860–863.
[7] B. Seckin, O.H. Yumusak, A. Tokmak, Comparison of two different starting doses of recombinant follicle stimulating hormone (rFSH) for intrauterine insemination (IUI) cycles in non-obese women with polycystic ovary syndrome (PCOS): a retrospective cohort study, J. Obstet. Gynaecol. 41 (2021) 1234–1239.
[8] S. Huang, R. Wang, R. Li, H. Wang, J. Qiao, B.W.J. Mol, Ovarian stimulation in infertile women treated with the use of intrauterine insemination: a cohort study from China, Fertil. Steril. 109 (2018) 872–878.

[9] M.F. Costello, M.L. Misso, A. Balen, J. Boyle, L. Devoto, R.M. Garad, R. Hart, L. Johnson, C. Jordan, R.S. Legro, R.J. Norman, E. Mocanu, J. Qiao, R.J. Rodgers, L. Rombauts, E.C. Tassone, S. Thangaratinam, E. Vanky, H.J. Teede, P.N. International, Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility, Hum Reprod Open (2019) hoy021.
[10] L. Quatrini, B. Ricci, C. Ciancaglini, N. Tumino, L. Moretta, Regulation of the immune system development by glucocorticoids and sex hormones, Front. Immunol. 12 (2021), 672853.
[11] L. Sun, J. Ye, Y. Wang, Q. Chen, R. Cai, Y. Fu, H. Tian, Q. Lyu, X. Lu, Y. Kuang, Elevated basal luteinizing hormone does not impair the outcome of human menopausal gonadotropin and medroxyprogesterone acetate treatment cycles, Sci. Rep. 8 (2018), 13835.
[12] R. Deswal, S. Nanda, A.S. Dang, Association of Luteinizing hormone and LH receptor gene polymorphism with susceptibility of Polycystic ovary syndrome, Syst. Biol. Reprod. Med. 65 (2019) 400–408.
[13] M.T. Le, V.N.S. Le, D.D. Le, V.Q.H. Nguyen, C. Chen, N.T. Cao, Exploration of the role of anti-Mullerian hormone and LH/FSH ratio in diagnosis of polycystic ovary syndrome, Clin. Endocrinol. 90 (2019) 579–585.
[14] M.M. Biljan, N.G. Mahutte, N. Dean, R. Hemmings, F. Bissonnette, S.L. Tan, Effects of pretreatment with an oral contraceptive on the time required to achieve pituitary suppression with gonadotropin-releasing hormone analogues and on subsequent implantation and pregnancy rates, Fertil. Steril. 70 (1998) 1063–1069.
[15] F. Coppola, E.R. Poti, L. Barusi, B. Ferrari, M.C. Salvarani, E. Vadora, Profound luteinizing hormone suppression induces a deleterious follicular environment during assisted reproduction technology, Fertil. Steril. 79 (2003) 459–460.
[16] M.A. Damario, L. Barmat, H.C. Liu, O.K. Davis, Z. Rosenwaks, Dual suppression with oral contraceptives and gonadotrophin releasing-hormone agonists improves in-vitro fertilization outcome in high responder patients, Hum. Reprod. 12 (1997) 2359–2365.
[17] E.M. Kolibianakis, E.G. Papanikolaou, M. Camus, H. Tournaye, A.C. Van Steirteghem, P. Devroey, Effect of oral contraceptive pill pretreatment on ongoing pregnancy rates in patients stimulated with GnRH antagonists and recombinant FSH for IVF. A randomized controlled trial, Hum. Reprod. 21 (2006) 352–357.
[18] J. Tesarik, C. Mendoza, Effects of exogenous LH administration during ovarian stimulation of pituitary down-regulated young oocyte donors on oocyte yield and developmental competence, Hum. Reprod. 17 (2002) 3129–3137.
[19] A. Weghofer, S. Munne, W. Brannath, S. Chen, D. Barad, J. Cohen, N. Gleicher, The impact of LH-containing gonadotropin stimulation on euploidy rates in preimplantation embryos: antagonist cycles, Fertil. Steril. 92 (2009) 937–942.
[20] Y. Gao, S. Jiang, L. Chen, Q. Xi, W. Li, S. Zhang, Y. Kuang, The pregnancy outcomes of infertile women with polycystic ovary syndrome undergoing intrauterine insemination with different attempts of previous ovulation induction, Front. Endocrinol. 13 (2022), 922605.
[21] B. Wang, Z. Li, Comparison of dual-trigger and human chorionic gonadotropin-only trigger among polycystic ovary syndrome couples who underwent controlled ovarian stimulation and intrauterine insemination: a retrospective cohort study, Medicine 102 (2023), e32867.
[22] Chinese Medical Association, Chapter of Assisted Reproductive Technology and Sperm Bank. Standard Operating Procedure of Clinical Techniques, first ed., People's millitary medical press, Beijing, 2010.
[23] E.M. Kolibianakis, C. Albano, J. Kahn, M. Camus, H. Tournaye, A.C. Van Steirteghem, P. Devroey, Exposure to high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotropin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy, Fertil. Steril. 79 (2003) 873–880.
[24] R.J. Norman, D. Dewailly, R.S. Legro, T.E. Hickey, Polycystic ovary syndrome, Lancet 370 (2007) 685–697.
[25] R. Rebar, H.L. Judd, S.S. Yen, J. Rakoff, G. Vandenberg, F. Naftolin, Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome, J. Clin. Invest. 57 (1976) 1320–1329.
[26] S.K. Blank, C.R. McCartney, J.C. Marshall, The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome, Hum. Reprod. Update 12 (2006) 351–361.
[27] L. Regan, E.J. Owen, H.S. Jacobs, Hypersecretion of luteinising hormone, infertility, and miscarriage, Lancet 336 (1990) 1141–1144.
[28] R. Homburg, A. Eshel, N.A. Armar, M. Tucker, P.W. Mason, J. Adams, J. Kilborn, I.A. Sutherland, H.S. Jacobs, One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation, BMJ 298 (1989) 809–812.
[29] G. Oner, Muderris, II, Assessment of ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with familial Mediterranean fever, Eur. J. Obstet. Gynecol. Reprod. Biol. 170 (2013) 449–451.
[30] S. Panchal, C. Nagori, Comparison of anti-mullerian hormone and antral follicle count for assessment of ovarian reserve, J. Hum. Reprod. Sci. 5 (2012) 274–278.
[31] R.H. Hunter, B. Cook, T.G. Baker, Dissociation of response to injected gonadotropin between the Graafian follicle and oocyte in pigs, Nature 260 (1976) 156–158.
[32] T.G. Baker, Oogenesis and ovulation, in: R.V. Short (Ed.), Austin CR, Cambridge University Press, Cambridge, 1972.
[33] R. Homburg, N.A. Armar, A. Eshel, J. Adams, H.S. Jacobs, Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome, BMJ 297 (1988) 1024–1026.