Gynecology and Obstetrics Clinical Medicine 1 (2021) 205–210

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

Research article

The effect of serum luteinizing hormone on trigger day with a GnRH antagonist protocol in IVF/ICSI treatment

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ARTICLE INFO

Keywords:
Gonadotrophin-releasing hormone antagonist
Controlled ovarian stimulation
Luteinizing hormone
Live birth rate

ABSTRACT

Objective: To investigate the effect of serum luteinizing hormone (LH) on trigger day with a Gonadotrophin-releasing hormone (GnRH) antagonist protocol in patients receiving *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment for pregnancy outcomes.

Methods: We retrospectively reviewed the medical documents of patients receiving IVF/ICSI with fresh embryo transfers from the Reproductive Medicine Center of Peking University People's Hospital between January 2016 and December 2018.730 patients were included and divided into three groups by their serum LH level determined on trigger day. All patients were categorized into Group A, Group B, and Group C based on LH concentrations <1.0 IU/L, 1.0–5.0 IU/L, and from 5.0 to 10.0 IU/L on trigger day during the cycle, respectively. Comparisons were made between the three groups.

Results: There was a significant difference in implantation rates between Group A and Group C (24.8% versus 40.1%, respectively, $P < 0.05$). The clinical pregnancy rates (39.3% versus 54.3%, respectively, $P = 0.078$) and live birth rate (LBR) (32.1% versus 46.5%, respectively, $P = 0.116$), though the differences were not significant. Multivariate logistic regression analysis showed that the OR of Group C for clinical pregnancy (OR = 1.849, $P = 0.040$) and for LBR (OR = 1.915, $P = 0.034$) were significant using Group A as the base level.

Conclusions: Our study has demonstrated that patients with higher serum LH levels (5.0–10.0 IU/L) on trigger day in the GnRH antagonist protocol may confer better clinical outcomes than those with lower LH levels (<1.0 IU/L).

1. Introduction

Gonadotrophin-releasing hormone (GnRH) antagonist protocols have been widely used in *in vitro* fertilization (IVF) treatments for the past twenty years,[1] although it has recently emerged as an IVF treatment in China. As opposed to the GnRH agonist that can achieve long-term suppression of pituitary activity, GnRH antagonists could only temporarily inhibit the secretion of pituitary gonadotrophins (Gns) by competitive occupancy of the GnRH receptors in the pituitary gland. So, compared to the long-term GnRH agonist protocol, the new GnRH antagonist protocol is more convenient, safe, and clinically effective.[2] In controlled ovarian stimulation (COS), the low level of LH concentration inhibited by GnRH antagonists could have negative effects on follicular development and endometrial receptivity,[3,4] while poor control of serum LH may induce premature ovulation or follicle luteinization. Serum LH level was used to indicate proper oocyte maturation and endometrial development. As described by the two-Gn and two-cell hypothesis, adequate follicle-stimulating hormone (FSH) is necessary for follicular growth and moderate LH is essential for follicular maturation and/or improvement of the endometrium.[5] In our experience, using either GnRH agonists or GnRH antagonist protocols, some patients usually had a low LH level in different follicular phases. Thus, the suppression of LH secretion and accumulation can be similarly induced by GnRH agonist and GnRH antagonist administration. The resulting low LH levels are

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Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2021.11.004
Received 9 April 2021; Received in revised form 1 August 2021; Accepted 3 November 2021
Available online 26 November 2021

likely detrimental to the formation of the follicle oocyte complex.[6,7] Nevertheless, Pousias[8] reported that in the natural cycle of normal fertile women, serum LH levels were maintained at 5 and 10 IU/L during the middle and late stages of follicle development. Of course, serum LH levels over 10.0 IU/L indicate the occurrence of an LH surge. So, the serum LH threshold is currently controversial and the serum LH level during COS upon treatment with GnRH antagonists for optimal oocyte quality and endometrial receptivity is a point of concern. In 2016, Chen et al.[9] reported early pregnancy loss rates of 619 patients of the low and high LH groups undergoing IVF/ICSI with an antagonist protocol in their center. The low LH group exhibited a higher early pregnancy loss rate compared to the high LH group. However, they did not report more detailed pregnancy outcome comparisons between the two groups. Moreover, the LH level needed to be refined for further investigation of the threshold at which LH levels can affect pregnancy outcomes. The present study is based on patients who have received GnRH antagonist treatment at our center over the past three years. We collected data from 730 patients and separated them into groups defined by smaller intervals of LH levels on the patient's trigger day to determine the LH level range that conferred better clinical outcomes of IVF/ICSI and comprehensively assessed its association with pregnancy results.

2. Materials and methods

2.1. Study design

This is a retrospective, single-center cohort study. There was a total of 730 patients undergoing a GnRH antagonist protocol with fresh embryo transfers in the Reproductive Medicine Center of Peking University's People's Hospital between January 2016 and December 2018. Patients diagnosed with hypothalamic amenorrhea were excluded. In addition, patients with uterine factors disease which included an immature uterus, uterine mediastinum, uterine adhesions, a thin endometrium ($\leq$0.6 cm on trigger day), and submucous myoma of the uterus were excluded. Patients with LH $\geq$ 10.0 IU/L on trigger day were excluded. There were 25 patients with LH > 10IU/L. Due to the limited data, there was a large deviation in our statistical analyses. Moreover, the influence of the LH peak has been considered, so we excluded it. The 730 patients were divided into three groups: Group A (n = 84) <1.0 IU/L; Group B (n = 519) $\geq$ 1.0 IU/L to $\leq$5.0 IU/L; and Group C (n = 127) > 5.0 IU/L to $\leq$ 10.0 IU/L LH on trigger day. Other data used in the study included age, body mass index (BMI), causes of infertility, baseline follicle-stimulating hormone (bFSH), AMH (anti-Mullerian hormone), the initial and total dose of Gn, the duration of Gn stimulation, the dose of antagonist use, the concentration of estradiol (E_2) and progesterone (P) on trigger day, the rate of MII oocytes, the rate of 2 PN, the rate of fertility, the rate of good quality embryos, the number of good quality embryos, and the number of transferred embryos. The endpoint measurements were implantation rate, clinical pregnancy rate, early pregnancy loss rate, and live birth rate (LBR).

2.2. Ovarian stimulation protocol and luteal phase support

This study performed baseline FSH, LH, oestradiol, and progesterone determination and transvaginal ultrasonography except for bilateral ovarian cysts and pregnancy on day 2 of the cycle before the use of Gn for all patients. The starting dose was chosen based on a patient's age, BMI, baseline FSH concentration, antral follicle count, and AMH concentration. COS commenced on the 2nd day of the menstrual cycle for 4 or 5 consecutive days with a fixed starting dose of r-FSH (Gonal-F; Merck Serono Biopharma) at 150–450 IU for all subjects. The daily r-FSH dose was then adjusted according to ovarian responses. When at least one follicle reached 13–14 mm in diameter, GnRH antagonist (ganirelix; Organon, or cetrorelix acetate; Merck-Serono) was added to the stimulation protocol, which was a flexible GnRH antagonist protocol. When at least two leading follicles reached 18 mm in diameter, induction of final oocyte maturation was triggered either by 250 μg of recombinant human chorionic gonadotropin (rhCG) (Ovidrel; Merck Serono Biopharma) or by a combination of hCG (2000IU, im) and 0.2 mg of triptorelin (Decapeptyl; Ferring Pharmaceuticals). The choice of triggering method was based on the discretion of the attending physician. Oocyte retrievals were performed 36–38 h later. The embryos were graded using morphological criteria. An appropriate day 3 embryo had at least 6–10 cells with less than 20% fragmentation. A good day 5 blastocyst exhibited distinct trophectoderm and inner cell mass. All embryo transfers were performed on day 3 or day 5 after oocyte retrieval. The number of embryos transferred was decided by the clinician based on patient age and embryo quality, but was never over 2 embryos. Patients received progesterone supplements (progesterone, 60 mg, once a day, im) for luteal phase support. Serum β-hCG level at 14 days after embryo transfer of >5 IU/mL was considered to be a positive pregnancy. The presence of an intrauterine sac on ultrasonography at 4 weeks after embryo transfer was defined as clinical pregnancy. The LBR was defined as the delivery of at least one live-born child after the 28th week of pregnancy. Early pregnancy loss was defined as the loss of a clinical pregnancy with no fetal heart activity or disappearance of fetal heart activity before 12 weeks of gestation. The luteal phase support continued until the 12th week of gestation for all positive pregnancies.

2.3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 19.0). Continuous variables were presented as mean with standard deviation (SD). The independent *t*-test and the Mann–Whitney *U* test was applied with normal and non-normal distributions, respectively. If there was a statistical difference between the groups, we compared any two groups using the Bonferroni correction method for the α value. Categorical variables were presented as raw frequencies with corresponding percentages and were compared using a chi-square test or a Fisher exact test. $P < 0.05$ was considered statistically significant. A binary logistic regression model was used to analyze the potential associating factors of pregnancy outcome. The strength of relevance was presented as an odds ratio (OR) with 95% confidence intervals (CIs).

3. Results

There were a total of 730 IVF/ICSI patients included in our study. The mean age was 33.48 ± 4.54 years old, and the mean BMI was 23.18 ± 3.74 kg/m^2. The mean infertility duration was 3.50 ± 2.95 years. No differences were detected in age, infertility duration, infertility factors, BMI, bFSH, AMH, the initial dose of Gn, the total dose of Gn, duration of Gn, the dosage of GnRH antagonist, and endometrial thickness among the three groups (Table 1).

Table 2 shows the patient laboratory data among the three groups. There were no differences in the number of high-quality embryos and transferred embryos. There were significant differences in MII rate, fertility rate, 2 PN rate, and good quality embryo rate among them. After further pairwise comparisons, the good quality embryo rates were highest in Group C, and the differences were significant (11.0% vs 11.8% vs 14.5%, respectively, $P < 0.05$).

There was a significant difference in implantation rates between Group A and Group C (24.8% versus 40.1%, respectively, $P < 0.05$). There were no differences in early pregnancy loss rates among these three groups. The clinical pregnancy rates (39.3% versus 54.3%, $P = 0.078$) and LBR (32.1% versus 46.5%, $P = 0.116$) were not significantly different between Group A and Group C (Table 3).

The OR and 95% CI of all factors from multivariate logistic regression for clinical pregnancy, pregnancy loss, and LBR are shown in Tables 4–6 Compared to Group A, the clinical pregnancy (OR = 1.849, $P = 0.040$) and the LBR (OR = 1.915, $P = 0.034$) of Group C were significantly higher. Moreover, the pregnancy loss was not significantly different.

Table 1
Comparison of patients' characteristics between different groups χ±MD/n (%).

LH on trigger day	Group A (LH < 1,n = 84)	Group B (1 = LH ≤ 5,n = 519)	Group C (5 < LH ≤ 10,n = 127)	The Total (n = 730)	*P* value
age (years)	33.02 ± 4.01	33.55 ± 4.50	33.51 ± 5.02	33.48 ± 4.54	0.616
infertility duration (years)	3.34 ± 2.71	3.47 ± 2.96	3.75 ± 3.04	3.50 ± 2.95	0.536
infertility factors					
PCOS	5 (6.0)	49 (9.4)	13 (10.2)	67 (9.2)	0.532
endometriosis n (%)	4 (4.8)	31 (6.0)	12 (9.4)	47 (6.4)	0.288
tubal factor	43 (51.2)	232 (44.7)	46 (36.2)	321 (44.0)	0.083
male factor	23 (27.4)	176 (33.9)	48 (37.8)	247 (33.8)	0.293
BMI(kg/m^2)	22.74 ± 3.46	23.25 ± 3.86	23.18 ± 3.40	23.18 ± 3.74	0.514
baseline FSH(IU/L)	7.59 ± 2.94	8.70 ± 5.04	8.69 ± 2.92	8.58 ± 4.53	0.393
AMH(ng/ml)	2.98 ± 2.27	3.03 ± 4.49	3.88 ± 9.23	3.15 ± 5.23	0.565
initial dose of Gn (IU)	220.09 ± 67.02	223.22 ± 70.85	208.23 ± 72.96	220.27 ± 70.92	0.104
total dose of Gn (IU)	2335.86 ± 813.52	2285.07 ± 699.46	2200.20 ± 664.40	2276.25 ± 707.70	0.345
duration of Gn (days)	9.82 ± 1.71	9.40 ± 1.70	9.39 ± 2.10	9.45 ± 1.80	0.120
dosage of GnRH-anti (mg)	0.88 ± 0.29	0.95 ± 0.34	0.99 ± 0.38	0.95 ± 0.34	0.213
trigger day E_2 (pg/ml)	2227.21 ± 1308.99	1788.44 ± 1177.82	1720.71 ± 1114.51	1827.51 ± 1190.53	0.004*
trigger day LH(IU/L)	0.74 ± 0.19	2.59 ± 1.08	6.66 ± 1.26	3.09 ± 2.03	0.000*
trigger day P (ng/ml)	0.79 ± 0.34	0.86 ± 0.60	1.01 ± 0.34	0.87 ± 0.54	0.003*
endometrial thickness (mm)	9.95 ± 2.01	9.69 ± 1.95	9.86 ± 2.16	9.75 ± 1.99	0.429
Trigger					0.032*
HCG	60.7 (51)[a]	51.6 (268)	42.5 (54)[b]	51.1 (373)	
HCG + GnRHa	39.3 (33)[c]	48.4 (251)	57.5 (73)[d]	48.9 (357)	

*p < 0.05 a vs b: P = 0.01; c vs d: P = 0.01 (p < 0.0167) BMI: body mass index, AMH: anti Mullerian hormone, Gn: gonadotrophins, GnRH-anti: GnRH antagonist, E_2: estradiol, LH: luteinizing hormone, P: progesterone, HCG: human chorionic gonadotropi, GnRHa: GnRH agonist.

Table 2
Comparison of protocol characteristics between different groups.

LH on trigger day	Group A (LH < 1,n = 84)	Group B (1 = LH ≤ 5,n = 519)	Group C (5 < LH ≤ 10,n = 127)	*P* value
MII rate (%)	78.2	74.2	73.50	0.04*
fertility rate (%)	79.9[a]	75.7[b,c]	79.3[d]	0.004*
2 PN rate	69.1[a]	63.7[b]	66.1	0.01*
good quality embryo rate	11.0[a]	11.8[c]	14.5[b,d]	0.03*
Number of good quality embryo [$M(P_{25},P_{75})$]	1 (0,2)	1 (0,2)	1 (0,2)	0.113
Number of transferred embryo (χ±MD)	1.92 ± 0.42	1.90 ± 0.36	1.87 ± 0.34	0.553

*p < 0.05 a vs b: p < 0.0167.c vs d: p < 0.0167.

4. Discussion

An increasing number of scholars have found that LH plays an important role in the COS. As the two-gonadotrophin and two-cell hypothesis details, LH induces the transformation of progesterone to androgens, which are important substrates for estrogen production, and thus mediates the microenvironment of the oocyte during development.[9] Currently, the LH threshold and its relevance in clinical practice are a topic of debate. Westergaard, Merviel, and Propst et al.[10–12] used an LH threshold of 0.5 mIU/mL to define the low LH group. However, they found that low serum LH concentration has opposite effects on oocyte maturation, pregnancy rates, and reproductive outcomes. Whereas, Chen et al.[9] showed that the cut-off between the normal LH group and the low LH group was set at 0.8 IU/L. Furthermore, it was shown that low LH levels are related to poorer oocyte/embryo or endometrium quality with a resultant increase in spontaneous abortions. In our study, 730 patients were included and divided into three groups by their serum LH levels on trigger day based on our clinical experience. The high-quality embryo rates and the implantation rates appeared highest in LH5-10IU/L, and the differences were significant compared to Group LH < 1IU/L and LH1-5IU/L. According to our multivariate logistic regression analysis, the clinical pregnancy (OR = 1.849, *P* = 0.040) and the LBR (OR = 1.915, *P* = 0.034) of LH5-10IU/L were significantly higher compared to LH < 1IU/L. Our study showed that patients with 5–10 IU/L of serum LH on trigger day under a GnRH antagonist regimen might have better clinical outcomes than patients with 1–5 IU/L of LH.

4.1. A low serum LH level can negatively affect follicular quality and pregnancy outcome

Physiologically, LH activity is crucial for proper folliculogenesis.[13] Indeed, in the late follicular phase, granulosa cells are receptive to LH

Table 3
Comparison of pregnancy outcome between different groups.

Serum LH On trigger day	Group A (LH < 1,n = 84)	Group B (1 = LH ≤ 5,n = 519)	Group C (5 < LH ≤ 10,n = 127)	*P* value
implantation rate	24.8% (40/161)[a]	32.2% (317/986)	40.1% (95/237)[b]	0.005*
clinical pregnancy rate	39.3% (33/84)	45.5% (236/519)	54.3% (69/127)	0.078
early pregnancy loss rate	9.1% (3/33)	8.9% (21/236)	8.7% (6/69)	0.998
live-birth rate	32.1% (27/84)	41.4% (215/519)	46.5% (59/127)	0.116

*p < 0.05 a vs b: p < 0.0167.

which can sustain follicular growth even when exogenous FSH administration was discontinued.[14] Circulating endogenous concentrations of LH are reduced in women undergoing treatment with GnRH agonists (GnRHa) and ovarian stimulation with recombinant human FSH (r-hFSH)[15] A prospective randomized study demonstrated that the low LH on hCG day has negative effects in down-regulated women and LH supplementation seemed to have a beneficial effect on the maturation of and ability to fertilize oocytes. However, the pregnancy rate was not different.[15] In our study, all of our patients were treated with an antagonist regimen. The MII, fertility, and 2 PN rates were slightly higher in LH < 1IU/L than LH5-10 IU/L, but there was no statistical difference. Moreover, the good quality embryo rates, implantation rates, clinical pregnancy rate, and LBR of LH < 1IU/L were significantly lower among these three groups. Therefore, we posit that a low serum LH level on trigger day in patients undergoing GnRH antagonist treatment is associated with lower follicular quality and lower rates of successful pregnancy.

Table 4
The multivariate logistic regression analysis of confounding factors for LBR.

Factor	Odds ratio (95% CI)	*P* value
Age, yd		
≤30		
30 < age<35	1.141 (0.781–1.665)	0.495
35 = age<40	0.633 (0.402–0.996)	0.048*
≥40	0.393 (0.183–0.846)	0.017*
BMI, kg/m^2	0.971 (0.862–1.094)	0.629
<18.5		
18.5–23.9	1.586 (0.833–3.019)	0.160
≥24	1.731 (0.884–3.390)	0.110
PCOS	0.550 (0.313–0.966)	0.038*
endometriosis	0.962 (0.519–1.783)	0.903
Total dosage of Gn	1.000 (1.000–1.000)	0.869
trigger day LH		
LH < 1		
1 = LH ≤ 5	1.518 (0.918–2.509)	0.104
5 < LH ≤ 10	1.915 (1.051–3.490)	0.034*
trigger day E_2		
E_2 < 1000		
1000 = E_2 ≤ 2000	0.862 (0.582–1.275)	0.456
2000 < E_2 ≤ 3000	0.862 (0.555–1.339)	0.509
3000 < E_2 ≤ 4000	0.739 (0.407–1.342)	0.320
E_2 > 4000	0.741 (0.376–1.458)	0.385
trigger day P	1.064 (0.800–1.416)	0.670
Trigger		
HCG		
HCG + GnRHa	1.012 (0.868–1.180)	0.881

Table 5
The multivariate logistic regression analysis of confounding factors for clinical pregnancy.

Factor	Odds ratio (95% CI)	*P* value
Age,y		
≤30		
30 < age<35	1.044 (0.717–1.520)	0.822
35 = age<40	0.644 (0.412–1.005)	0.053
≥40	0.341 (0.161–0.724)	0.005*
BMI,kg/m^2		
<18.5		
18.5–23.9	1.763 (0.935–3.324)	0.080
≥24	1.735 (0.894–3.367)	0.103
PCOS	0.848 (0.496–1.449)	0.546
endometriosis	1.226 (0.665–2.259)	0.514
Total dosage of Gn	1.000 (1.000–1.000)	0.619
trigger day LH		
LH < 1		
1 = LH ≤ 5	1.281 (0.789–2.078)	0.316
5 < LH ≤ 10	1.849 (1.030–3.322)	0.040*
trigger day E_2		
E_2 < 1000		
1000 = E_2 ≤ 2000	0.829 (0.563–1.222)	0.343
2000 < E_2 ≤ 3000	0.838 (0.543–1.295)	0.427
3000 < E_2 ≤ 4000	0.650 (0.361–1.170)	0.151
E_2 > 4000	0.620 (0.317–1.210)	0.161
trigger day P	1.038 (0.779–1.382)	0.801
Trigger		
HCG		
HCG + GnRHa	1.062 (0.913–1.236)	0.437

*P < 0.05, significant difference.

Table 6
The multivariate logistic regression analysis of confounding factors for pregnancy loss.

Factor	Odds ratio (95% CI)	*P* value
Age,y		
≤30		
30 < age<35	0.717 (0.269–1.912)	0.506
35 = age<40	2.162 (0.734–6.365)	0.162
≥40	1.034 (0.108–9.890)	0.977
BMI,kg/m^2		
<18.5		
18.5–23.9	1.229 (0.146–10.328)	0.850
≥24	1.331 (0.150–11.798)	0.797
PCOS	3.028 (0.979–9.366)	0.054
endometriosis	2.720 (0.850–8.703)	0.092
Total dosage of Gn	1.000 (0.999–1.000)	0.389
trigger day LH		
LH < 1		
1 = LH ≤ 5	0.851 (0.222–3.258)	0.814
5 < LH ≤ 10	0.862 (0.175–4.238)	0.855
trigger day E_2		
E_2 < 1000		
1000 = E_2 ≤ 2000	0.831 (0.318–2.167)	0.704
2000 < E_2 ≤ 3000	0.935 (0.328–2.666)	0.899
3000 < E_2 ≤ 4000	0.425 (0.047–3.811)	0.445
E_2 > 4000	0.000	0.998
trigger day P	0.687 (0.222–2.131)	0.516
Trigger		
HCG		
HCG + GnRHa	1.068 (0.711–1.602)	0.752

4.2. *The mechanisms of how LH level affects pregnancy outcome*

As we know, in the middle-later follicular phase, the serum LH level can affect the quality of follicles, and a premature rise of LH or elevated LH in this phase will induce premature ovulation or even luteinization of follicles, resulting in reduced follicular quality.[3] Tesarik et al. showed that the low LH level in the middle-later follicular phase could affect endometrium receptibility for implantation.[4] Their data suggested that the direct action of LH or HCG on uterine LH receptors was needed to support both endometrial growth and uterine receptivity in the implantation window. Moreover, Licht et al. reported that LH/HCG receptors are detectable in the endometrium throughout the reproductive cycle and confer a peri-implantation increase in receptor number.[16] With LH/HCG receptors increased, adequate LH levels are needed during the progression of implantation. Tesarik et al. have also proposed that endometrial receptivity could be affected by the down regulation of GnRH agonists in the frozen embryo transfer cycles due to low LH levels.[4] Also, hCG could decrease the apoptosis of endometrial stromal cells.[17,18] Finally, low LH levels could also increase the progesterone concentration to affect the endometrium development in the late follicular phase of COS.[19] The premature surge of progesterone is related to the asynchrony of the implantation window and the development of the embryo, which negatively affected embryo implantation in the fresh embryo transplantation cycles.[20] These studies theoretically explained the importance of an adequate level of LH on trigger day for the development of oocytes

and endometrial receptivity, as demonstrated by the outcomes of this study.

4.3. The serum LH level of 5–10 IU/L patients may have better pregnancy outcomes

In 2016, Chen et al.[9] showed that there were significantly increased early pregnancy loss rates (31.1% versus 16.3%, $P = 0.012$) when LH concentration was lower than 0.8 IU/L in the GnRH antagonist cycle. Their study took patients of LH ≤ 0.8IU/L as the reference group and they focused on the effect of low LH in the GnRH antagonist cycle. Their study showed a negative impact of low LH on the establishment of early pregnancy. However, there was no significant difference in the LBR between their two study groups (23.7% versus 30.4%). We considered that the possibility of the difference in LBR might be diminished due to the large range of LH observed in the LH > 0.8 IU/L group. Whereas, our study further investigated and subdivided the serum LH levels into our groups on trigger day with LH > 1 IU/L, and found that not only can the level of LH in the GnRH antagonist cycle be too low, which matches the conclusions reached by Chen et al.,[9] but we also found that when the LH levels of patients were in the range of 5–10 IU/L, the clinical pregnancy and LBR increased significantly. The study reported by Yang et al.[21] found that by supplementation with 75–150u LH in patients with LH ≤ 0.8 IU/L at the middle and late follicular phases, the early pregnancy loss rate decreased significantly (11.5% versus 26.7%, $P < 0.05$), but there was no difference in clinical pregnancy rate (47.7% versus 43.1%, $P > 0.05$), while LBR was not reported. Moreover, the study stratified the findings for early-onset and late-onset low LH patients and found that supplementing LH in the middle and late follicular phase significantly reduced early pregnancy loss in the patients with early-onset low LH (3.3% versus 29%, $P < 0.05$). While in the late-onset low LH group, there is no statistical difference in the early pregnancy loss rate between the supplemented and non-supplemented groups. At the same time, there was no significant difference in the clinical pregnancy rate between the two subgroups. This study also suggested the importance of a certain level of LH in the GnRH antagonist cycle for reducing early pregnancy loss. The supplementation of LH in a low LH cycle is usually 75–150 IU/d. We speculated that LH supplementation can improve some of the negative effects of clinical outcomes caused by low LH levels. However, the serum level of LH has difficulty in reaching the level of 5–10 IU/L in the late follicular phase, which is also the level of the natural menstrual cycle. Liu et al.[22] suggested that LH Levels may be used as an indicator for the time of antagonist administration in GnRH antagonist protocols and patients with sustained low LH levels (LH max <4 IU/L) during COS might not require antagonist administration. A certain level of LH in the follicle phase, probably more than 1 IU/L on trigger day, was necessary for better results in GnRH antagonist cycles. Therefore, we think that maintaining a relatively high level of LH in the antagonist cycle and remaining close to the level of the natural follicular development cycle is beneficial to the treatment outcomes of patients.

Our study has its limitations due to its retrospective nature and single-center cohort study design. The sample size might also be inadequate for decisive conclusions. In the COS, LH levels were indeed dynamic. Due to the characteristics of medical treatment in China, patients were subject to periodic return visits so continuous determination of serum LH level was greatly limited. In addition, our data were retrospective, so comprehensive data of LH levels could only be obtained on trigger day. The biochemical pregnancy and late abortion were not conducted in our study. On one hand, the definition of biochemical pregnancy and the relationship between late abortion and hormone levels were not related. On the other hand, more reports suggested that late abortion was related to multiple pregnancies, infection, cervical problems, and other factors.[23] To further confirm the beneficial effect of increasing and maintaining a high level of LH while not causing premature LH peaking is one of the important future research areas in COS.

5. Conclusions

This study has demonstrated that patients with higher serum LH levels on trigger day in a GnRH antagonist regimen might have better clinical outcomes than those with lower LH. Moreover, our study has proposed that Chinese patients with 5–10 IU/L of serum LH on trigger day undergoing a GnRH antagonist regimen may have better clinical outcomes for IVF/ICSI. To the best of our knowledge, this is the first study that has proposed this conclusion. However, we still need a more substantial sample size and multi-center research efforts to make randomized control trials (RCTs) and an in-depth study on the mechanism of action.

Authors' contributions

Yanru Hou: Project development, Data Collection, Data analysis, Manuscript writing. Li Tian: Project development, Data analysis, Manuscript editing. Huixin Liu: Data analysis. Jiajia Ai: Data Collection. Yanbin Wang: Data management. Huan Shen: study supervising.

Availability of data and material

Not applicable.

Funding

This work was supported by the National Key Technology R&D Program of China (nos. 2019YFC1005200 and 2019YFC1005201).

Ethics approval and consent to participate

Ethics Committee of Peking University People's Hospital that approved the study and the committee's reference number was 2020PHB063-01. And all participants gave informed consent.

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.

Acknowledgements

None.

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