rLH/rFSH Combination Improved Cumulative Live Birth Rate in Patients With LH Over-Suppression Following GnRH Agonist Pituitary Down-Regulation Compared to rFSH or hMG Alone: A Retrospective Cohort Study With Propensity Score Matching

Ansu Tu
　Chengdu Jinjiang District Maternal and Child Health Hospital

Lihong Geng
　Chengdu Jinjiang District Obstetrics and Gynecology Hospital

Ying Zhong (✉ zhongy@jxr-fertility.com)
　Chengdu Jinjiang District Obstetrics and Gynecology Hospital

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Research Article

Abstract

Purpose

The suppression of luteinizing hormone (LH) in patients undergoing gonadotropin-releasing hormone agonist (GnRH-a) pituitary down-regulation may cause LH deficiency which may impact follicular development. However, little is known about effect of LH adding in patients with LH over-suppression. This study to investigate the effects of different gonadotropins on the cumulative live birth rate (CLBR) in the patients with LH over-suppression after GnRH-a pituitary down-regulation.

Methods

This retrospective study used propensity score-matching methodology to compare CLBR, as the primary endpoint, in the patients with LH over-suppression after different GnRH-a pituitary down-regulation regimens, including recombinant follicle stimulating hormone (rFSH) combined with recombinant LH (rLH), or using rFSH alone, or human menopausal gonadotropin (hMG) alone. The secondary endpoints included biochemical pregnancy rate, clinical pregnancy rate, and live birth rate in fresh embryo transfer cycles.

Results

A total of 88 patients were enrolled after matching: 22 patients in the rFSH+rLH group, 44 in the rFSH group, and 22 in the hMG group. The CLBR of the rFSH+rLH group was significantly higher than that of the rFSH and hMG groups (19/22, 86.4% vs. 25/44, 56.8%, P = 0.014; vs. 7/22, 31.8%, P < 0.001). Moreover, the rFSH group had a higher CLBR than the hMG group (P = 0.048). There were no significant differences in any of the secondary endpoints (all P > 0.05).

Conclusion

Exogenous rLH supplementation achieved a higher CLBR than rFSH or hMG alone among patients with LH over-suppression; furthermore, rFSH alone was superior to hMG alone for CLBR.

Background

With the development of in vitro fertilization-embryo transfer technology, different controlled ovarian stimulation regimens have been used for different patients with the aim of achieving improved clinical outcomes; however, some drug-induced situations needed careful monitoring, such as gonadotropin-releasing hormone agonist (GnRH-a) induced luteinizing hormone (LH) over-suppression. GnRH-a is one of the most commonly used medications in assisted reproductive technologies (ART) [1]. However, a profound suppression of LH can be noted in some patients who undergo GnRH-a pituitary down-regulation [2].

The physiological need for LH in follicular development is known; however, the influence of the LH decline on ART outcomes is still controversial. Some studies indicate that a decreased LH level is directly associated with a lower live birth rate [3, 4], while another came to a controversial conclusion [5].

It is therefore uncertain whether LH supplementation should be recommended to those with LH over-suppression. Conclusions from early studies are divided: some confirm the effectiveness of LH supplementation [6], while others conclude that supplementation with recombinant LH does not increase success rates [7]. Therefore, this study sets out to further investigate the effects of LH supplementation, using the statistical method of propensity score-matching (PSM), on the cumulative live birth rate of patients with LH over-suppression after GnRH-a pituitary down-regulation.

Methods

Subjects

This study was a single-center, retrospective, three-armed, cohort study using propensity score matching analysis. From September 1, 2013 to August 31, 2017, patients with LH over-suppression after GnRH-a pituitary down-regulation at the Jinjiang Maternal and Child Health Hospital, Chengdu, China, were screened for this study. With reference to a previous study [7], while the date of LH measurement was adjusted according to our practice, LH over-suppression was defined as the LH level on the day of Gn initiation being $\geq$ 50% lower than that at baseline, which was tested on the 2nd or 3rd day of the previous menstrual cycle. These participants were naturally grouped according to the administration of different ovarian stimulation drugs: recombinant follicle stimulating hormone (rFSH; GONAL-f®, Merck Serono SA, Succursale d'Aubonne) combined with recombinant LH (rLH; Luveris®, Merck Serono SA); rFSH (GONAL-f®) alone; and human menopausal gonadotropin (hMG; Lebaode®, Lizhu Medicine, Zhuhai, China) alone. Patients were matched using the PSM method at an adjusted ratio of 1:2:1 to meet the optimal balance between patient number and matching results. The cumulative live birth rate and other clinical data of patients under different ovarian stimulation regimens were analyzed. This study had waived informed consent owing to its retrospective nature and it did not involve any privacy information.

Treatment methods

All treatments were based on decisions by clinicians, derived from individual patient profiles. For patients in the rFSH + rLH group, GONAL-f and Luveris were coadministered at a fixed dose of 150 IU:75 IU for ovarian stimulation until trigger day. Patients in the rFSH and hMG groups were given rFSH or hMG alone, respectively, and the dose was adjusted according to ovarian response. All other treatments followed the routine processes of GnRH-a long protocols [8].

Data collection

In this study, the data collected included age, body mass index (BMI), and duration of infertility. Baseline sex hormone tests were carried out on the 2nd or 3rd day of the previous menstrual cycle, which included LH, FSH, estradiol (E2), progesterone (P), prolactin (PRL), and antral follicle count (AFC). Some

information related to fertility history was recorded, such as the number of previous live births, number of previous ART cycles, and any causes of infertility. The LH level tests were repeated on the day of Gn administration, and the actual LH decrease from baseline to the 1st day of Gn administration, and also the percentage of LH decrease, were calculated. The following measurements were related to drug administration, examinations, and clinical outcomes during the ART: average daily FSH dose and total FSH dose, endometrial thickness, the number of fertilized oocytes obtained, the number of available embryos, the number of high quality embryos, and the rate of high quality embryos.

Outcome measures

The primary outcome was the cumulative live birth rate, which was defined as: the proportion of deliveries with at least one live birth resulting from one initiated ART cycle, including all cycles in which fresh and/or frozen embryos were transferred, until one delivery with a live birth occurred or until all embryos were used, whichever occurred first [9]. The secondary outcomes included FSH dose, biochemical pregnancy rate, clinical pregnancy rate, and live birth rate in the fresh embryo transfer cycle. FSH dose was the overall amount of FSH (rFSH, GONAL-f®) in rFSH + rLH group and rFSH group, or the equivalent FSH dose in hMG group (hMG, Lebaode®) used in the study period. The biochemical pregnancy rate was defined as the number of pregnancies per 100 initiated cycles, that were diagnosed by the detection of serum beta human chorionic gonadotropin (HCG). The clinical pregnancy rate referred to the number of pregnancies per 100 cycles that were diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. Live birth rate in the fresh embryo transfer cycle was defined as the number of deliveries that resulted in at least one live birth, expressed per 100 attempts of fresh embryo transfer cycles. Some other outcomes were compared, in order to address any possible reasons for differences in outcome, including endometrial thickness at the time of HCG injection, the number of fertilized oocytes obtained, embryo number, high quality embryos, and high quality embryo rate.

Statistical analysis

R software (version 3.60) was used for statistical analyses. Propensity score-matching (using the principle of nearest neighbor matching) was carried out by matching the following data: age, BMI, primary or secondary infertility, duration and causes of infertility, history of previous pregnancies or live births, number of ART cycles, baseline hormone levels, AFC, absolute value and percentage decrease of LH, and endometrial thickness on trigger day. The continuous data were recorded as mean ± standard deviation and the Kruskal-Wallis test was used. The discontinuous data were recorded as a percentage (%) and analyzed using the chi-square test, or Fisher's exact test if the sample size was too small. For multiple comparisons, each value was compared by one-way ANOVA, and followed by pairwise comparison using the 1-sided Fisher's exact test.

Results

General patient characteristics at baseline

A total of 21 925 pituitary down-regulation cycles using GnRH-a were screened in this study. There were 15 347 cycles where LH was decreased by > 50% on Gn initiation day. Among these cycles, only 22 cycles used rFSH + rLH 150 IU:75 IU fix dose from the first day to the trigger day, and all of them were included in the PSM. According to the results of matching, there were a further 44 patients included in the rFSH mono-therapy group, and 22 in the hMG mono-therapy group, resulting in a total of 88 patients involved in this study. The baseline data of patients and LH changes (both actual decrease and decrease rate) on the day of Gn initiation showed no significant difference among the three groups. The details are listed in Table 1.

Table 1
Patient characteristics

Index	rFSH + rLH group (n = 22)	rFSH group (n = 44)	hMG group (n = 22)	P
Age (y)	27.9 ± 2.3	27.9 ± 3.5	28.8 ± 3.7	0.59
BMI	21.2 ± 2.1	21.4 ± 2.8	21.6 ± 2.3	0.89
Years of infertility (y)	3.5 ± 2.3	3.9 ± 2.9	4.1 ± 2.6	0.70
FSH (mIU/ml)	6.1 ± 0.9	6.1 ± 1.3	6.9 ± 2.0	0.21
E2 (nmol/24h)	49.6 ± 13.0	49.5 ± 29.3	66.1 ± 47.2	0.13
P (nmol/L)	0.7 ± 0.3	1.0 ± 2.3	0.7 ± 0.3	0.61
PRL (mIU/L)	297.8 ± 160.9	223.9 ± 114.3	230.1 ± 155.2	0.13
LH (IU/L)	4.4 ± 1.3	4.5 ± 1.3	4.6 ± 1.4	0.98
AFC	23.5 ± 6.5	23.2 ± 7.2	20.1 ± 5.4	0.14
No. of previous pregnancies	1.1 ± 1.1	1.0 ± 1.4	0.9 ± 1.2	0.60
No. of previous live births	0.1 ± 0.5	0.1 ± 0.3	0.1 ± 0.2	0.79
No. of previous ART cycles	0.0 ± 0.0	0.1 ± 0.4	0.2 ± 0.7	0.14
Proportion of primary infertility	11/22(50%)	21/44(47.7%)	13/22(59.1%)	0.68
Causes of infertility				0.79
Fallopian tube	10(45.5%)	18(40.9%)	7(31.8%)	
Ovary	1(4.5%)	2(4.5%)	1(4.5%)	
spouse	2(9.1%)	5(11.4%)	4(18.2%)	
Multiple factors	9(40.9%)	16(36.4%)	10(45.5%)	
Unknown reason	0	3(6.8%)	0	
The decrease of LH on Gn day	3.7 ± 1.2	3.6 ± 1.2	3.6 ± 1.4	0.92
The decrease rate of LH in trigger on Gn day	81.4 ± 8.5%	78.1 ± 8.2%	76.0 ± 11.9%	0.22

Note: BMI: Body Mass Index; FSH: follicle stimulating hormone; E2: estrogen; P: progesterone; PRL: prolactin; LH: luteinizing hormone; AFC: antral follicle counts.

Primary outcome

The results showed that the cumulative live birth rate of the rFSH + rLH group was higher than that of the rFSH group or the hMG group (ANOVA result P < 0.001, pairwise comparison rFSH + rLH group 19/22, 86.4% vs. rFSH group 25/44, 56.8%, P = 0.014; vs. hMG group 7/22, 31.8%, P < 0.001). At the same time, the cumulative live birth rate of the rFSH group was also higher than that of the hMG group (P = 0.048).

Secondary outcomes

The daily average dose (150.0 ± 0 and 147.5 ± 23.2 vs. 208.5 ± 29.4) and the total dose (1445 ± 150 and 1340 ± 255 vs. 2277 ± 539) in the rFSH + rLH group and the rFSH group, were both significantly less than that of the hMG group (all P < 0.001). However, the biochemical pregnancy rate, clinical pregnancy rate, and live birth rate in the fresh cycle showed no statistical differences among the three groups (P > 0.05, Table 2) The results also showed that there were no statistical differences in endometrial thickness, the number of fertilized oocytes obtained, the number of available embryos, number of high quality embryos, or high quality embryo rate (P > 0.05).

Table 2
Primary outcomes of cumulative live birth rate and the secondary outcomes

Index	rFSH + rLH group (n = 22)	rFSH group (n = 44)	hMG group (n = 22)	P
Cumulative live birth rate	19(86.4%)*#	25(56.8%)$	7(31.8%)	< 0.001
Average dose of FSH(IU)	150.0 ± 0.0*	147.5 ± 23.2*	208.5 ± 29.4	< 0.01
Total dose of FSH(IU)	1445 ± 150*	1340 ± 255*	2277 ± 539	< 0.01
Fresh cycle biochemical pregnancy rate	4(18.2%)	5(11.4%)	4(18.2%)	0.67
Fresh cycle clinical pregnancy rate	4(18.2%)	4(9.1%)	3(13.6%)	0.57
Fresh cycle Cumulative live birth rate	4(18.2%)	4(9.1%)	3(13.6%)	0.57
Endometrial thickness at the time of HCG injection	10.9 ± 1.7	9.9 ± 2.1	10.7 ± 1.8	0.09
The no. of fertilized oocytes obtained	18.4 ± 6.1	20.8 ± 11.3	16.4 ± 8.4	0.33
Embryo number	13.8 ± 5.6	16.5 ± 10.0	13.8 ± 6.7	0.58
High quality embryos	5.6 ± 3.9	6.0 ± 5.2	5.8 ± 4.6	0.99

Note: FSH: follicle stimulating hormone; HCG: human chorionic gonadotropin; *: P < 0.001 when compared with hMG group; #: P = 0.014 when compared with rFSH group; $: P = 0.048 when compared with hMG group.

Discussion

With this PSM study, we aimed to achieve more certain conclusions than previous cohorts or case control studies. Although the samples size was small, it was statistically capable of reflecting differences in effectiveness on CLBRs among the three regimens, given the obvious differences. The outcomes of this study showed that both the rFSH + rLH therapy and the rFSH therapy alone significantly increased the cumulative live birth rate in LH over-suppression patients when compared with hMG therapy; it also resulted in a significantly reduced dose of FSH. Furthermore, rFSH + rLH therapy produced a better outcome than rFSH alone.

Previously, there has been controversy over the value of supplemental exogenous LH during ART. Evidence from early studies suggested that LH did not affect clinical pregnancy outcome [10–12]. On the other hand, several studies had given a confirmation on the clinical value of exogenous LH [13, 14]. We supposed the timing of LH supplementary was the key point of this issue. In previous studies, LH were administrated late follicular phase [3], or at the day LH decrease to < 0.5 mU/ml [15]. The LH administration was carried out during the whole course in this study, since rFSH initiate, in rFSH + rLH group. One reason was that we defined the LH over suppression by the data at Gn initiation day and baseline. It is possible to distinguish the patients occurred LH over suppression since the treatment started. The other reason was that we believe exogenous LH supplyment as early as possible could improve the clinical outcomes more. The results of this study showed that rFSH + rLH therapy significantly increased the cumulative live birth rate in LH over-suppression patients when compared with rFSH treatment alone. Similar results have been reported elsewhere [16–18]. Sonntag et al. report that long-term use of GnRH-a can lead to low levels of endogenous LH [19], thus it is important to supplement exogenous LH in patients with low LH levels [20]. Previous studies also found that patients with low serum LH levels achieved better clinical pregnancy rates after adding exogenous LH [15, 21–24]. Franco et al. report that supplementation with rLH significantly increases the number of fertilized oocytes obtained and the rate of cumulative live births [25]. In the current study, patients whose LH level decreased by ≥ 50% on the day of Gn initiation were included as subjects. The results of this study further validated the significant effect of rLH on maternity outcomes in patients with LH over-suppression after GnRH-a pituitary down-regulation.

The secondary outcomes, including biochemical pregnancy and clinical pregnancy in fresh cycles, showed no difference between the three groups. Furthermore, endometrial thickness at the time of HCG injection, or the number of fertilized oocytes obtained, or embryo number, were all similar among the three groups. It is not surprising that results in fresh cycles showed no difference, as the number of oocytes obtained, or embryo number, were more closely related to the effect of controlled ovarian hyperstimulation. However, these numbers were also similar in the current study. We propose that there are some unobserved factors that influence embryo or endometrial quality that result in an improved CLBR.

It is possible that some detailed differences in clinical practice, such as drugs administered from different manufacturers, might result in different conclusions. Furthermore, the definition of LH over-suppression might influence these results. Several efforts were made in this study to obtain a more certain conclusion;

for example, we clarified the definition of LH over-suppression, which was set at a decrease of ≥ 50%, to reduce the impact of individual factors, such as baseline extreme high or low LH. Furthermore, we also balanced both an actual decrease and a decrease in rate of LH level among the three groups using PSM. This definition differed from previous studies, and could therefore be a reason for the difference in results.

By comparing the hMG group and the other two groups, we found a significantly lower CLBR, which suggested a benefit from LH supplementation could only be achieved following administration of rLH. Even though hMG has an active function similar to rLH, the actual component of HCG is different from rLH, with the former being extracted from the urine of menopausal women while the latter comes from recombinant DNA technology. A previous study obtained a similar conclusion in women > 35 y [26]; the ongoing pregnancy rate was higher in an rFSH + rLH group than that in an hMG group (17.3% vs. 12.2%). However, in another study, the supplementation of LH did not show any significant improvement in clinical outcomes [27]. There should be differences in effectiveness between HCG and rLH based on their mechanism of action, thus we propose that the inconsistency of the effectiveness of rLH supplementation is related to the extent of decrease in LH. Interestingly, we found that the outcome in the rFSH alone group was also better than that in hMG group, a finding which has not been previously reported. The above-mentioned difference between rLH and HCG, patient characteristics of LH over-suppression, and probably the chosen outcome of CLBR, could be reasons why such obvious differences were found among the three groups.

Previous studies report that rLH supplementation reduces FSH dose requirement [28, 29]. In the current study, the FSH dose was reduced when compared with the hMG group, while it was not significantly decreased when rFSH alone was compared with rFSH + rLH; this may have been related to factors such as the relative fixed drug dose in clinical practice, and also the small sample size.

There were several limitations in this study. Firstly, this was only a retrospective study, not a randomized controlled trial; which leaves the opportunity for potential bias. Secondly, this study was a single-center clinical study with a small sample size. Additional multi-center clinical studies with larger sample sizes are warranted.

Conclusions

Exogenous rLH supplementation combined with rFSH in 2:1 fix dose from D1 administration can achieve a higher cumulative live birth rate than rFSH or hMG alone among patients with LH over-suppression following GnRH-a pituitary down-regulation.

Abbreviations

AFC antral follicle count

ART assisted reproductive technologies

BMI body mass index

CLBR cumulative live birth rates

E2 estradiol

GnRH-a gonadotropin-releasing hormone agonist

HCG human chorionic gonadotropin

hMG human menopausal gonadotropin.

P progesterone
PRL prolactin

PSM propensity score-matching

rFSH recombinant follicle stimulating hormone

rLH recombinant luteinizing hormone

Declarations

Ethics approval and consent to participate

This study had waived informed consent owing to its retrospective nature and it did not involve any privacy information.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request

Competing interests

None of the authors have any personal, financial, commercial, or academic conflicts of interest.

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