Original Article
The clinical application value of gonadotropin-releasing hormone antagonist combined with low-dose HCG regimen in patients with ovarian hyper-stimulation based on clinical characteristics and laboratory indicators

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Abstract: Objective: To explore the clinical application value of gonadotropin-releasing hormone antagonist (GnRH-A) combined with low-dose HCG regimen in patients with high ovarian response based on clinical characteristics and laboratory indicators. Methods: The clinical data of 305 patients who received IVF/ICSI in the Hechi People's Hospital Reproductive Medicine Center from March 2018 to December 2021 were retrospectively included, and all patients were treated with GnRH-A combined with low-dose HCG regimen protocol. The patients were separated into an ovarian hyper-response group and a normal ovarian reaction group according to their ovarian reactivity. Risk factors for ovarian hyper-response in IVF/ICSI patients were screened by univariate and multivariate logistic analysis. The ROC curve area was used to evaluate the prediction effect. Results: Of the 305 patients, 6 (1.97%) had poor ovarian reaction, 123 (40.33%) had ovarian hyper response, and 176 (57.70%) had normal ovarian reaction. The proportion of ovarian hyper response and normal ovarian reaction was 98.03% (299/305); the basic serum FSH level, AMH level, E_2 on HCG level on HCG injection day and the incidence of moderate to severe OHSS in the Ovarian hyper-response group were compared with those in the normal ovarian reaction group ($P < 0.05$). Logistic reversion analysis showed that AMH (OR = 1.246, 95% CI = 1.107-1.402), E_2 level on HCG injection day (OR = 1.050, 95% CI = 1.028-1.072) and P level on HCG injection day (OR = 5.831, 95% CI = 1.231-27.616) were factors for ovarian hyper response. Basal serum FSH (OR = 0.781, 95% CI = 0.647-0.94) and LH level on HCG injection day (OR = 0.594, 95% CI = 0.405-0.871) were negatively correlated with the occurrence of high response ($P < 0.05$). ROC curve analysis showed that AMH (AUC = 0.779), E_2 level on HCG injection day (AUC = 0.802), P level on HCG injection day (AUC = 0.636), combined detection (AUC = 0.843), AUC > 0.5. Among them, the prediction effect of joint detection is better. Conclusion: GnRH-A combined with low-dose HCG regimen is feasible for patients with ovarian hyper-response during IVF-ET/ICSI, and does not affect the implantation rate, clinical pregnancy rate, live birth rate, and early abortion rate of such patients. Combined detection of basal serum FSH, AMH, LH, E_2 and P levels on HCG injection day can effectively predict the occurrence of ovarian hyper-response.

Keywords: Antagonist regimen, high ovarian response, ovarian hyperstimulation syndrome, clinical outcome

Introduction

Controlled ovarian stimulation (COS) is an important part of IVF/ICSI-ET in assisted reproductive technology (ART), that is, by using follicle stimulating hormone (FSH) to recruit more follicles, bypassing the phenomenon of follicular atresia regulation and the advantage of a single follicle, it is possible to obtain multiple eggs [1, 2]. However, during ovulation induc-

tion, the ovary is too sensitive to human chorionic gonadotropin (HCG), resulting in high ovarian response [manifested as elevated level of luteinizing hormone (LH), serum estradiol (E_2) hormones, and multiple follicular development] [3]. Ovarian hyperstimulation syndrome (OHSS) is a complication caused by controlled hyperstimulation of ovulation (COH), which may even affect the patient's life and health [4]. According to the literature [5], moderate and severe OHSS

(3%-6%) occurs during the entire cycle of ovulation induction. In the ovarian hyperresponse population, OHSS occurred (14%-16%), and some even had the risk of thrombotic death. In order to avoid the occurrence of serious consequences, the application of HCG was often canceled, resulting in the inability to obtain eggs, which brought great loss to patients' finances, body and time. Therefore, while ensuring that the number of eggs and embryos is excellent, and a good pregnancy outcome, the appropriate ovulation induction method plays a significant role in preventing the occurrence of OHSS.

Studies have shown that GnRH-A can reduce the dosage of Gonadotropin (Gn) and the incidence of OHSS in patients with polycystic ovary syndrome (PCOS), which is increasingly favored by clinicians [6]. However, other study has also reported that GnRH-A treatment is prone to insufficient luteal function, resulting in a decrease in clinical pregnancy rate and an increase in early abortion rate [7]. Based on this, scholars began to focus on improving pregnancy outcomes through luteal support, including the use of GnRH-A combined with low-dose HCG luteal support [8]. However, there is no consensus on whether GnRH-A regimen can reduce the incidence of moderate/severe OHSS in patients with ovarian hyper response and achieve excellent clinical outcomes. At the same time, there are few reports about the factors that affect the therapeutic effect of combination therapy. This study aimed to the clinical application value of gonadotropin-releasing hormone antagonist (GnRH-A) combined with low-dose HCG regimen in patients with high ovarian response based on clinical characteristics and laboratory indicators.

Materials and methods

Basic information

The clinical data of 305 patients who underwent IVF/ICSI treatment in Hechi People's Hospital Reproductive Medicine Center from March 2018 to December 2021 were retrospectively analyzed. Inclusion criteria: ① Patients who underwent IVF/ICSI treatment; ② Patients who received COS by using GnRH-A combined with low dose HCG; ③ Patients with an age ≤ 35 years old. Exclusion criteria: ① Patients with severe hydrosalpinx (or vaginal B-ultrasound examination on the day of trans-

plantation, showing the presence of hydrosalpinx); ② Patients with a history of uterine diseases (such as intrauterine adhesions, endometriosis, uterine and adenomyosis, and endometritis); ③ Patients or their her husband with abnormal karyotype; ④ Patients with a history of recurrent abortion; ⑤ Patients with endocrine complications such as hypothyroidism or hyperthyroidism.

The diagnostic criteria of ovarian hyperstimulation [9]: ① Number of eggs taken during superovulation cycle (> 15), or the cycle was cancelled due to excessive follicular development; ② The number of follicles (diameter > 13 mm, and > 20) was detected during superovulation; ③ Occurrence after controlled ovarian hyperstimulation (moderate/severe OHSS); ④ During the process of superovulation (E_2 > 5000 ng/L). Those who meet any one of above criteria were assigned to an ovarian hyper response group. Those with a number of 5-15 oocytes and serum E_2 > 1835 pmol/L (500 pg/mL) on HCG injection day were assigned to a normal ovarian reaction group [10]. Patients with poor ovarian reaction, that is the number of retrieved oocytes was less than 5 and/or the serum E_2 level was less than 1835 pmol/L (500 pg/mL) on the day of HCG injection, were excluded [11]. This study was approved by the Ethics Committee of Hechi People's Hospital. Since this study was a retrospective study, data were anonymized and informed consent was not required.

Methods

Gn (Gonafin, Merck Serono SA, 75 IU/cig) 150-225 U/d was started on the 2nd to 3rd day of natural cycle catamenia. The detailed initial dose can be combined with the patient's age, BMI, basic AMH, basic AFC, and ovarian reserve function. After 3-4 days, the follicular development was evaluated according to the results of vaginal B-ultrasound combined with serum E_2 detection, and the dose of Gn or LH was adjusted in time. When the dominant follicles (diameter ≥ 14 mm) and serum E_2 > 300 pg/ml, 0.25 mg/d GnRH-ant (SZK, Merck Serono SA, Switzerland) was subcutaneously injected; or when follicle diameter ≥ 18 mm and the number > 3 or follicle diameter ≥ 20 mm and number > 2, 2000-6000 IU HCG was injected for triggering. After about 37 h, the eggs were collected with the guidance of transvaginal ultrasound and incubated in an incubator.

Conventional in vitro fertilization (IVF) was selected according to the actual situation of patients. After fertilization (16-24 h), the eggs were observed, and the cleavage of embryos was observed later (66-68 h). If blastocyst culture was required, blastocyst development was examined at 116 h and 136 h after insemination to evaluate the morphology of embryos.

Clinically relevant indicators of the candidates were collected, including age, infertility years, body mass index (BMI), primary infertility, antral follicle count (AFC), basal serum LH, FSH, E_2, anti-muller hormone (AMH), initial Gn amount, total Gn, Gn administration days, FSH level on HCG injection day, LH level on HCG injection day, P level on HCG injection day, E_2 level on HCG injection day, endometrial thickness on HCG injection day, 2PN fertilization rate, cleavage rate, number of transplanted embryos, blastocyst proportion, implantation rate, clinical pregnancy rate, ectopic pregnancy rate, incidence of moderate to severe OHSS, early abortion rate, live birth rate.

Diagnostic criteria of moderate to severe OHSS

According to the 2017 Cochrane evidence-based medical guidelines [12], moderate OHSS diagnostic criteria: severe abdominal distension, abdominal pain, nausea and vomiting, and vaginal B-ultrasound examination showed paraovarian ascites, ovarian diameter 5-10 cm; severe OHSS: moderate OHSS symptoms are aggravated, including shortness of breath or difficulty, tension ascites, oliguria or anuria, difficult to relieve nausea, vomiting, rapid weight gain, hemodynamic abnormalities (such as hypoproteinemia, blood concentration, insufficient blood volume), liver and kidney dysfunction and electrolyte disorders, pericardial or pleural effusion, and severe complications (adult respiratory distress syndrome, acute renal failure, arrhythmia, thrombosis, etc.).

Statistical methods

SPSS 24.0 was used for data processing. The measurement data (subject to Gaussian distribution) were described as mean ± standard deviation ($\bar{x} \pm s$) and compared using t test. The enumeration data were described by rate/percentage (%) and compared using χ^2 test. Univariate and multivariate logistic regression analysis was used to find the risk factors affecting high ovarian response. The AUC under the ROC curve was used to evaluate the predictive accuracy of each risk factor for high ovarian response. P < 0.05 indicated statistical difference.

Results

Comparison of clinical characteristics between the ovarian hyper-response group and normal ovarian reaction group

A total of 305 patients treated with IVF/ICSI were included; among them, 6 (1.97%) had poor ovarian response, 123 (40.33%) had ovarian hyper-response that were classified as the ovarian hyper-response group, and 176 (57.70%) had normal ovarian reaction that were classified as normal ovarian response group. The proportion of ovarian hyper-response and normal ovarian reaction was 98.03% (299/305). Two of the six patients with low ovarian response underwent fresh embryo transfer, and no moderate or severe OHSS occurred, so they were removed. There were no statistical differences in age, BMI, proportion of primary infertility, duration of infertility, baseline serum E_2 and LH levels, initial Gn amount, total Gn amount, FSH/LH/endometrial thickness, P level on HCG injection day, cleavage rate, 2PN fertilization rate, number of embryos transferred, blastocyst proportion, ectopic pregnancy rate, implantation rate, early abortion rate, clinical pregnancy rate and live birth rate between the ovarian hyper-response group and the normal ovarian reaction group (all *P* > 0.05). The baseline serum FSH level, AMH level, E_2 level on HCG injection day and the incidence of moderate to severe OHSS in the ovarian hyper-response group differed significantly to those in the normal ovarian reaction group (all *P* < 0.05), are shown in **Table 1**.

Univariate and multivariate logistic analysis of risk factors of ovarian hyper-response

In this study, the above factors that may affect ovarian hyper-responsiveness were analyzed by univariate analysis, and the variables with *P* < 0.05 after analysis were further included in the multivariate logistic regression analysis. The results showed that AMH level (OR = 1.246, 95% CI = 1.107-1.402), E_2 level on HCG injection day (OR = 1.050, 95% CI = 1.028-1.072), P level on HCG injection day (OR = 5.831, 95% CI = 1.231-27.616) were risk factors for ovarian

Table 1. Comparison of clinical characteristics between the ovarian hyper-response group and normal ovarian reaction group

Index	Ovarian hyper-response group (n = 123)	Normal ovarian reaction group (n = 176)	t/χ^2	P
Age	29.61±3.84	29.80±4.03	0.409	0.683
Infertility years (years)	3.85±1.13	3.92±1.25	0.496	0.621
BMI (Kg/m²)	22.10±3.20	21.87±3.25	0.606	0.545
Primary infertility (%)	84 (68.29)	115 (65.34)	0.283	0.594
AFC (a)	21.75±4.75	20.22±4.55	2.810	0.005
Baseline serum LH (IU/L)	7.63±2.35	7.26±2.37	1.333	0.184
Baseline serum FSH (IU/L)	6.02±1.49	6.71±1.64	3.716	< 0.001
Baseline serum E_2 (pg/ml)	22.49±2.56	22.60±3.25	0.314	0.754
AMH (ng/ml)	11.73±3.30	8. 41±2.86	9.297	< 0.001
Initial Gn amount (IU)	137.43±42.55	143.08±46.87	1.065	0.288
Total Gn (IU)	1799.89±565.01	1848.33±600.72	0.703	0.483
Gn days (d)	10.79±2.64	12.77±2.70	6.297	< 0.001
FSH on HCG injection day (IU/L)	11.03±3.82	11.52±3.89	1.080	0.281
LH on HCG injection day (IU/L)	2.28±0.79	2.46±0.81	0.910	0.057
P on HCG injection day (mg/L)	0.69±0.20	0.65±0.19	1.753	0.081
E_2 on HCG injection day (pg/ml)	6065.52±2013.20	4040.17±1500.33	9.964	< 0.001
Endometrial thickness on HCG injection day (cm)	1.05±0.21	1.07±0.21	0.810	0.418
2PN fertilization rate (%)	79 (64.22)	114 (64.77)	0.009	0.923
Cleavage rate (%)	121 (98.37)	173 (98.29)	0.003	0.958
Number of embryos transferred (a)	2.10±0.32	2.04±0.28	1.718	0.087
Proportion of blastocysts (%)	13 (10.57)	17 (9.66)	0.066	0.797
Implantation rate (%)	47 (38.21)	86 (48.86)	3.327	0.068
Clinical pregnancy rate (%)	67 (54.47)	84 (47.73)	1.317	0.251
Ectopic pregnancy rate (%)	1 (0.81)	1 (0.57)	0.065	0.798
The incidence of moderate to severe OHSS (%)	12 (9.76)	5 (2.84)	6.457	0.011
Early abortion rate (%)	16 (13.01)	12 (6.82)	3.268	0.071
Live birth rate (%)	67 (54.47)	99 (56.25)	0.093	0.761

Notes: BMI: body mass index; AFC: antral follicle count; LH: luteinizing hormone; FSH: follicle stimulating hormone; E_2: estradiol; P: progesterone; AMH: anti-Mullerian hormone; OHSS: ovarian hyperstimulation syndrome.

hyper-response. Baseline serum FSH level (OR = 0.781, 95% CI = 0.647-0.942) and LH level on HCG injection day (OR = 0.594, 95% CI = 0.405-0.871) were protective factors of ovarian hyperresponsiveness (P < 0.05), as shown in **Table 2**.

Prediction effect

In the ROC curve, it is generally believed that AUC > 0.5 indicates predictive power. In this study, ROC curve analysis showed that baseline serum FSH (AUC = 0.378) and LH level on HCG injection day (AUC = 0.406) had an AUC < 0.5, indicating poor prediction effect; while AMH (AUC = 0.779), E_2 level on HCG injection day

(AUC = 0.802), P level on HCG injection day (AUC = 0.636), and combined detection (AUC = 0.843) had an AUC > 0.5, indicating good prediction value. Among them, the prediction effect of joint detection was better, as shown in **Table 3** and **Figure 1**.

Discussion

In clinical reproductive work, GnRH-A regimen has been gradually applied in clinical practice, because it can not only reduce the incidence of OHSS, but also lower the dosage of Gn and the cycle cancellation rate during ovulation induction [13, 14]. According to the literature [15], 70% of centers adopt GnRH-A program abroad,

Table 2. Univariate and multivariate logistic analysis of risk factors for ovarian hyper-response

Variable	Single factor analysis		Multiple-factor analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.988 (0.932-1.047)	0.680	-	-
Infertility years (years)	0.952 (0.785-1.154)	0.616	-	-
BMI	1.022 (0.952-1.098)	0.544	-	-
Primary infertility	1.599 (0.987-2.593)	0.057	-	-
AFC	1.049 (0.996-1.106)	0.076	-	-
Baseline serum LH	1.067 (0.967-1.178)	0.195	-	-
Baseline serum FSH	0.761 (0.654-0.884)	< 0.001	0.799 (0.659-0.969)	0.022
Baseline serum E_2	0.988 (0.914-1.067)	0.753	-	-
AMH	1.447 (1.309-1.598)	< 0.001	1.237 (1.098-1.392)	< 0.001
Initial Gn amount	0.997 (0.992-1.002)	0.286	-	-
Total Gn amount	0.999 (0.995-1.003)	0.480	-	-
Gn administration days	0.967 (0.911-1.027)	0.280	-	-
Hormone levels on HCG injection day				-
LH level on HCG injection day	0.653 (0.480-0.890)	0.007	0.595 (0.400-0.885)	0.010
E_2 level on HCG injection day	1.067 (1.053-1.092)	< 0.001	1.053 (1.031-1.076)	< 0.001
P level on HCG injection day	6.992 (2.059-23.743)	0.002	5.988 (1.252-28.640)	0.025
Endometrial thickness on HCG injection day	0.606 (0.198-1.855)	0.380	-	-

Notes: BMI: body mass index; AFC: antral follicle count; LH: luteinizing hormone; FSH: follicle stimulating hormone; E_2: estradiol; P: progesterone; AMH: anti-Mullerian hormone; OHSS: ovarian hyperstimulation syndrome.

and the program has become the main program orientation for high-response high-risk groups.

Shen et al. [16] found that in patients with high ovarian response to GnRH-a plus different doses of HCG, the high-quality embryo rate, embryo numbers, high-quality embryos and oocytes obtained by GnRH-a plus low-dose HCG were higher than those of GnRH-a alone. It also indicates that for IVF/ICSI cycles, high ovarian responders have a higher rate of high-quality embryos applied to this treatment regimen, a lower incidence of moderate to severe OHSS, and a lower rate of miscarriage. Another study by Daniel et al. showed that using the GnRH-a+HCG trigger increased the number of frozen embryos in patients compared to patients using the GnRH-a trigger, leading to an increase in clinical pregnancy rates. However, it should be noted that 2.9% of patients using the GnRH-a+HCG trigger developed OHSS, although this difference was not statistically significant [17]. In this study, GnRH-A combined with low-dose HCG regimen was applied to 305 patients undergoing IVF/ICSI treatment, and it was found that 40.33% of these patients had ovarian hyper-responsiveness and 57.70% had normal ovarian reaction. Among them, the inci-

dence of moderate to severe OHSS in the ovarian hyper-responsiveness group was significantly higher than that in the normal ovarian reaction group (9.76% vs 2.84%). Consideration may be related to the small number of cases studied. If the occurrence of ovarian hyperresponse can be effectively avoided, the normal ovarian response can be obtained, and a good pregnancy outcome can be obtained. At the same time, the results also found that there were no significant differences in the implantation rate, clinical pregnancy rate and live birth rate between the normal ovarian response group and the ovarian hyperresponsiveness group. And the early abortion rate of the ovarian hyper-response group was about twice that of the normal ovarian response group, but there was no statistical difference (P > 0.05). This is consistent with the above research reports [14, 16].

The results of multivariate logistic regression analysis in this study showed that AMH, E_2 level on HCG injection day and P level on HCG injection day were independent risk factors for ovarian hyper-response (P < 0.05). The reason may be that AMH is a specific combination of preantral follicles and small antral follicles, which is a relatively close and indirect regulatory factor

Table 3. AUC and 95% CI confidence interval of risk factors

Risk factors	AUC	Standard error	P	95% CI
Baseline serum FSH	0.378	0.032	< 0.001	0.314-0.441
LH level on HCG injection day	0.406	0.034	0.006	0.340-0.472
AMH	0.779	0.028	< 0.001	0.725-0.834
E_2 level on HCG injection day	0.802	0.027	< 0.001	0.749-0.855
P level on HCG injection day	0.636	0.033	< 0.001	0.571-0.701
Combined detection	0.843	0.024	< 0.001	0.795-0.891

Notes: LH: luteinizing hormone; FSH: follicle stimulating hormone; AMH: anti-Mullerian hormone; E_2: estradiol; P: progesterone.
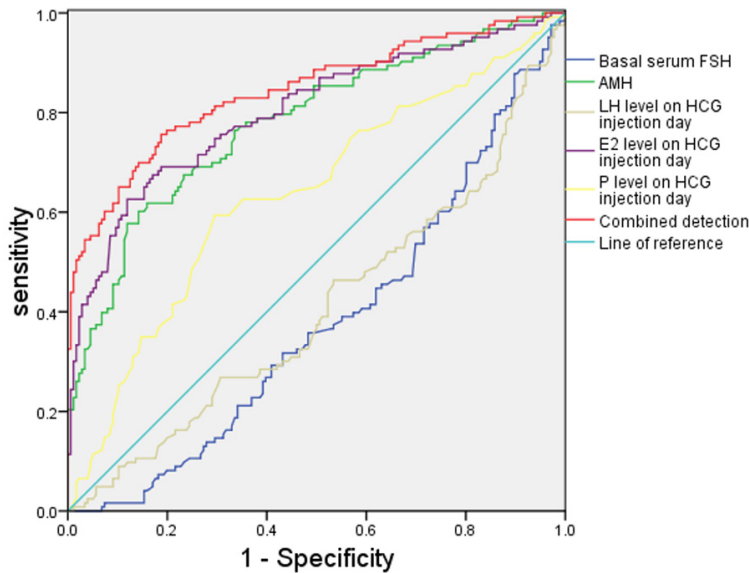

Figure 1. ROC analysis of high ovarian response. Notes: LH: luteinizing hormone; FSH: follicle stimulating hormone; AMH: anti-Mullerian hormone; E_2: estradiol; P: progesterone.

that can clearly reflect the primordial follicles. The expression of AMH is relatively stable and not affected by the menstrual cycle. Study has shown that AMH has become an indicator of female ovarian reserve function [18]. PCOS is a disease in which small follicles continue to accumulate and cannot mature. Compared with the normal population, the number of small antral follicles and preantral follicles in the ovary of PCOS patients increases more significantly. Relevant studies have shown that [19], AMH levels can be high in PCOS patients. Muharam et al. [20] found that serum AMH level was related to the number of antral follicles (2-5 mm), and the level of serum AMH in PCOS patients was 2-4 times higher than that in non-PCOS patients. Literature shows that

[21, 22] AMH can effectively predict PCOS. Consistent with some research results, the increase of P level on HCG injection day is a risk factor for the occurrence of high ovarian response, and the increase of this index is related to the increase of E_2 level and the increase of follicle number. The high level of P on HCG injection day can decrease the clinical pregnancy rate and cleavage blastocyst rate, and also affect the pregnancy rate, which leads to the increase of abortion rate in patients with high ovarian response [23, 24]. At present, the E_2 value on the day of HCG injection is often regarded as the peak of E_2 concentration, which is an indicator of ovarian response [25]. Clinically, the risk of OHSS is often evaluated by measuring the E_2 value and the number of follicles on the day of HCG injection. In this study, compared with the E_2 value on the day of HCG injection in the normal ovarian response group, the ovarian hyper-response group was significantly higher. Multivariate logistic regression showed that it was a risk factor, which confirmed that the sensitivity of these patients to exogenous Gn increased. In polycystic ovary, most of them developed follicles, which can cause some undeveloped follicles to develop when stimulated. In the process of follicular cell proliferation, androstenedione (ASD) and testosterone (T) will be produced in large quantities. Under the action of normal amount of FSH, endogenous estrogen will also be produced in large quantities, and then the sensitivity of follicles to FSH will also increase, thus promoting the development of more undeveloped follicles and increasing estrogen levels [26].

The levels of sex hormones on the 2nd to 4th day of natural menstrual cycle are the baseline sex hormones (including LH, E_2, FSH, serum inhibin A and B, etc.). LH and FSH in women can

stimulate follicular maturation, and the two coordinate to promote estrogen secretion [27]. Inhibin is secreted by ovarian granulosa cells, which can feedback inhibit the secretion of FSH in the anterior pituitary. Bancsi et al. [28] demonstrated that high baseline FSH level was associated with decreased ovarian reserve function. The study found that baseline serum FSH level was one of the predictors [29]. High level FSH indicates a decrease in ovarian response to exogenous stimulation. This study found that compared with the baseline serum FSH level in the normal ovarian response group, its level in the high response group was lower, and multivariate analysis also found that the baseline FSH level was negatively correlated with ovarian hyperresponsiveness, that is, the higher the baseline FSH level, the less likely ovarian hyperresponsiveness occurs. At present, some foreign scholars believe that the normal level of LH can maintain the secretion of hormones and the normal development of follicles [30]. When LH is in a low level, it can lead to the increase of exogenous LH addition time, the increase of drug dosage, and even the increase of early abortion rate. Yim [31] said that when the serum LH level exceeds 1 IU/L in controlled ovarian hyperstimulation (COH) of IVF-ET, it can meet the needs of oocyte development, fertilization and embryonic development. In the comparison of clinical data in this study, the LH level on the day of HCG injection in the ovarian hyper-response group was lower than that in the normal ovarian reaction group, and multivariate analysis also found that the LH level on the day of HCG injection was negatively correlated with the ovarian hyper-response.

In this study, ROC curve analysis showed that AMH, E_2 level on HCG injection day, P level on HCG injection day, and combined detection (AUC = 0.843) had an AUC > 0.5, indicating good prediction value. Among them, the prediction effect of joint detection was better, AUC was 0.843. It is suggested that the combined detection of AMH, E_2 level on the day of HCG injection and P level on the day of HCG injection can effectively predict the occurrence of high ovarian response after GnRH-A combined with low-dose HCG regimen. Due to the retrospective nature and small number of case samples, there may be some bias in the research results. In the future, prospective studies with larger sample size should be conducted to further validate the results.

Conclusion

GnRH-A combined with low-dose HCG regimen is feasible for patients with ovarian hyper-response during IVF-ET/ICSI, and does not affect the implantation rate, clinical pregnancy rate, live birth rate, and early abortion rate of such patients. Combined detection of basal serum FSH, AMH, LH, E_2 and P levels on HCG injection day can effectively predict the occurrence of ovarian hyper-response.

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Disclosure of conflict of interest

None.

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