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Original Article

Prevention and treatment of OHSS by administration of GnRH antagonist in the early luteal phase of controlled ovarian hyperstimulation cycles

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Abstract: To investigate the treatment effect of gonadotropin releasing hormone (GnRH) antagonist in the early luteal phase on ovarian hyperstimulation syndrome (OHSS) for in vitro fertilization-embryo transfer (IVF-ET). Retrospective analysis was conducted on 162 patients, who underwent IVF-ET using standard long protocol. More than 20 oocytes were retrieved, and fresh embryo transfer was canceled in these patients. The patients were divided into the antagonist group (n=82) and the control group (n=80), depending on whether GnRH antagonist was used after ovum pick-up (OPU). Serum estradiol in both groups decreased after OPU. Compared to the control group, it decreased more in antagonist group on day 2 after OPU ($P<0.05$). Menstrual duration in the antagonist group was significantly shortened by three days. The diameter of the bilateral ovaries in the antagonist group was significantly reduced on day 2 after OPU compared to the control group. The incidence of severe OHSS was significantly lower in the antagonist group than in the control group. In contrast, the incidence of mild OHSS was significantly higher in the antagonist group than in the control group. GnRH antagonist administration in the early luteal phase can effectively prevent and treat OHSS in IVF-ET.

Keywords: Gonadotropin releasing hormone antagonist, in vitro fertilization-embryo transfer (IVF-ET), ovarian hyperstimulation syndrome

Introduction

In vitro fertilization-embryo transfer (IVF-ET) has been widely used as an effective mean to treat infertility. However, the patients constantly suffered from some complications, such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. OHSS, an iatrogenic disease, has drawn widespread attention in clinical practice. OHSS can be divided into early and late OHSS. Early OHSS, which is triggered by human chorionic gonadotropin (HCG) during ovarian stimulation cycles, usually occurs between 3 and 7 days after HCG injection, or within 14 days if pregnancy fails. Most of late OHSS are triggered by endogenous HCG and occur 12-17 days after OPU [1, 2]. In the treatment cycles, the incidence of OHSS is approximately 3%-8%. The incidence of moderate and severe OHSS is 3%-6% and 0.1%-2% respectively [3]. OHSS is inevitable in controlled ovarian hyperstimulation (COH) cycles and severe OHSS is even life-threatening. Instead of fresh embryo transfer, frozen-thawed embryo transfer is one of the important ways to prevent OHSS in high-risk patients [4]. However, GnRHa long protocol is the widely used regimen. Early OHSS still happens in this protocol even though whole embryo freezing is carried out after HCG triggering. Therefore, prevention of OHSS remains an issue to be addressed in clinical practice of assisted reproduction. The GnRH antagonist protocol is suggested to treat it and some studies showed it is a safe and effective treatment for women undergoing in vitro fertilization (IVF) [5-8]. Lainas et al reported that 3 cases of severe OHSS happened in patients with polycystic ovary syndrome (PCOS) on day 6 after OPU and were improved considerably after 3 days of GnRH antagonist administration [9]. It suggested that administration of GnRH antagonist in the luteal phase could treat early OHSS

Table 1. Comparison of basic information

Basic condition	The antagonist group (n=82)	The control group (n=80)	T or x^2	P*
Ages (year)	27.96±3.49	28.83±4.40	1.38	0.17
Duration of infertility (year)	3.63±2.40	3.95±3.15	0.71	0.47
The dose of Gn (IU)	1974±562	1829±451	1.81	0.07
The days of Gn (day)	10.00±1.43	9.74±1.15	1.28	0.2
BMI (kg/m^2)	21.55±3.75	21.46±3.48	0.16	0.87
Basic FSH (mIU/ml)	6.33±2.01	6.59±1.63	0.92	0.36
Basic LH (mIU/ml)	5.70±3.85	5.27±3.03	0.8	0.42
The number of occytes retrival	27.49±6.85	28.21±9.44	0.56	0.58
The number of 2PN	16.30±6.09	14.80±6.28	1.55	0.12
The number of blastocyst freezed	9.93±5.42	8.19±4.86	2.15	0.03*
The etiology of infertility				
Primary infertility	47	42	0.38	0.54
Secondary infertility	35	38		
Tubal factor	37	40	0.39	0.53
Endometriosis	5	3	0.48	0.49
Anovulation	18	16	0.09	0.76
Male factor	15	14	0.02	0.89
Both factor	4	3	0.12	0.72
Unexplationed infertility	3	4	0.18	0.67

*P<0.05 was considered statistically significant.

Table 2. Serum estrogen level

Basic condition	The antagonist group (n=82)	The control group (n=80)	*t*	*P**
E2 of HCG (ng/L)	12925±2811	12961±2622	0.08	0.93
E2 of OPU (ng/L)	6994±3570	7543±3546	0.98	0.37
E2 of 2 days afer OPU (ng/L)	3314±2673	4006±2950	0.97	0.12

*P<0.05 was considered statistically significant.

effectively. In the present study, we investigated the treatment effect of gonadotropin releasing hormone (GnRH) antagonist in the early luteal phase on ovarian hyperstimulation syndrome (OHSS) for in vitro fertilization-embryo transfer (IVF-ET).

Material and method

Patients

A retrospective analysis was conducted in 162 patients who received IVF/ICSI at our clinic, from Junuary 1, 2015 to September 30, 2015. Inclusive criteria were as follows: 1) The patients received IVF/ICSI in our center; 2) The protocol was long protocol; 3) More than 20 oocytes were retrieved; 4) fresh embryo transfer was concealed.

Ovarian stimulation

All of the patients in this study underwent the standard long GnRH ag nist protocol. The patients were treated with Triptorelin Acetate (triptorelin, Ferring, Switzerland), at daily dose of 0.05 mg s.c., from the mid-luteral phase. Controlled ovarian stimulation was performed with 150-300 IU/d recombinant follicle-stimulating hormone (Gonal-F Merck Serono, Germany, or Puregan, Nertherlands). When three or more dominant follicles (>18 mm in diameter) appeared, 10000 IU human chorionic gonadotropin (hCG) was administered. Transvaginal oocytes retrieval under ultrasound guidance was done 34-36 hours after hCG administration.

Grouping

In the present study, the data of 162 patients who underwent IVF/ISCI in our fertility center were retrospectively reviewed. More than 20 oocytes were retrieved, fresh embryo transfer cancellation and whole embryo freezing were carried out in these patients. All of the 162 patients were given hydroxyethyl starch, aspirin, and dexamethasone. The patients were divided into two groups: the antagonist group (n=82) and the control group (n=80), depending on whether GnRH antagonist was used after ovum pick-up (OPU). Cetrorelix Acetate (Cetrotide, MerckSerono) were used in the patients of antagonist group after OPU, at 0.25 mg subcutaneous injection for 3 days. All of the patients were back to our clinic 2 day after OPU.

The classification criteria of OHSS

The classification of OHSS was referred to Golan classification standard: [10].

Table 3. Comparison of the serum estrogen decline percentage

Basic condition	The antagonist group (n=82)	The control group (n=80)	T	P*
Decline of E2 in OPU (E2 (HCG) -E2 (OPU)/E2(HCG))	0.48±0.19	0.43±0.22	1.33	0.19
Decline of E2 in 2 days after OPU (E2 (OPU) -E2 (OPU+2)/E2(OPU))	0.53±0.18	0.45±0.28	0.97	0.03*

*P<0.05 was considered statistically significant.

Table 4. The menses and mean diameter of bilateral ovaries

Basic condition	The antagonist group (n=82)	The control group (n=80)	T	P*
Mean menstrual duration (d)	9.3±1.17	12.23±1.35	-14.71	<0.001*
Mean diameter of bilateral ovaries (mm)	61.2±13.06	82.6±11.90	-10.90	<0.001*

*P<0.05 was considered statistically significant.

Table 5. The incidence of OHSS

	The antagonist group (n=82)	The control group (n=80)	X^2	P*
Mild OHSS	26 (31.7%)	11 (13.8%)	11.59	0.003*
Moderate OHSS	56 (68.3)	62 (53.3%)		
Severe OHSS	0	5 (6.3%)		

*P<0.05 was considered statistically significant.

Mild OHSS: abdominal distension, with or without nausea, vomiting, diarrhea and the ovarian diameter (less than 5 cm).

Moderate OHSS: ovarian diameter (5-12 cm), and ascites in ultrasound examination.

Severe OHSS: appearance of clinical symptoms of ascites and (or) pleural effusion, hypovolemia, hemoconcentration, increased blood viscosity, coagulation abnormalities, decreased renal perfusion and renal dysfunction.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0. Student t test was used to analyze the difference between groups. X^2 test was used to analyze the enumeration data. P<0.05 was considered statistically significant.

The procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. The experiment was accompanied by an approval by the local ethics committee.

Results

Comparison of basic condition

Depending on whether GnRH antagonist was used after ovum pick-up (OPU), the patients were divided into two groups: the antagonist group (n=82) and the control group (n=80). A retrospected analysis was performed. The basic condition of these patients was compared between two groups. As shown in **Table 1**, there was no statistical difference between these two groups in age, duration of infertility, basic FSH, basic LH, the dose of Gn, the days of Gn, BMI and the number of occytes retrival. Nor was there any statistical difference in etiology of infertility between the two groups.

The change of estrogen before and after GnRH antagonist adminstration

E2 levels of the patients were examined. The data showed that E2 levels in both groups significantly decreased after OPU. E2 level after 2 days of GnRH antagonist administration was lower than the control group, but there was no statistically difference. There was a statistically significant difference of estradiol level on day 2 after OPU in the antagonist group, which decreased more than that in the control group (**Table 2**). The analysis of the decline percentage in each group showed that GnRH antagonist administration decreased 8% more than that in the control group. The difference was statistically different (**Table 3**).

Comparison of the menses after OPU

No luteal support was used in both groups. Mean menstrual duration in the antagonist group was 9.3, and 12.23 in control group, menstrual duration was significantly shortened by 3 days in antagonist group. The difference was statistically different (**Table 4**).

Comparison of mean diameter of bilateral ovaries on 2 days after OPU

Due to the use of COH, the volume of ovaries increased after OPU. Mean diameter of the bilateral ovaries on day 2 after OPU in the antagonist group was 61.20 mm, and it was 82.60 mm in control group. The mean diameter was significantly reduced in antagonist group, compared to the control group (**Table 4**).

The effect of GnRH antagonist on mild and severe OHSS

As shown in **Table 5**, the incidence of severe OHSS was significantly lower in the antagonist group than in the control group. In contrast, the incidence of mild OHSS was significantly higher in the antagonist group than in the control group.

Discussion

Since Louise Brown was born in 1978, more than one million babies have been born through assisted reproductive technology (ART). ART is currently believed to be safe for newborns. However, OHSS is the most common and potentially dangerous complication during ovarian hyperstimulation, especially during IVF. This syndrome includes enlarged ovaries and a series of complications related to its severity. Prevention of OHSS remains an issue to be addressed in clinical practice of assisted reproduction. In this study we found that the diameter of the bilateral ovaries in the GnRH antagonist group was significantly reduced on day 2 after OPU compared to the control group. The incidence of severe OHSS was significantly lower in the antagonist group than in the control group. In contrast, the incidence of mild OHSS was significantly higher in the antagonist group than in the control group.

Early OHSS is a self-limited disease. If pregnancy fails, luteolysis followed by natural regression will start at the end of the cycle. Mild OHSS is considered as inevitable during ovarian hyperstimulation. In this case, most patients don't feel uncomfortable and require no treatment except avoiding strenuous activities. However, severe OHSS may lead to systemic lesions and is even life-threatening. Therefore, prevention and treatment of this iatrogenic disease, especially severe OHSS, is very important. Some therapeutic approaches are now emploued to prevent OHSS, including cycle cancellation, reducing gonadotropin (Gn) dose or using costing protocol [11]. reducing the dose of HCG or even inducing ovulation with GnRH-a trigger [12, 13], fresh embryo transfer cancellation [14], whole embryo freezing and administration of hydroxyethyl starch or aspirin to prevent exacerbation of OHSS. Nonetheless, the occurrence and progression of OHSS still can't be eradicated through these approaches.

OHSS is promoted by corpus luteum formation and inhibited by luteolysis. The way to reduce the severity and duration of OHSS relies on inhibiting corpus luteum formation while promoting luteolysis. Studies showed that GnRH antagonist administration in the luteal phase leaded to an earlier luteolysis [15]. The GnRH antagonist protocol was suggested to treat it and some studies showed it was a safe and effective treatment for women undergoing in vitro fertilization (IVF) 5 Studies showed that 40 patients, diagnosed with severe OHSS on day 5 after OPU received GnRH antagonist administration from day 5 to 8 after OPU. The ovarian volume, ascites, hematocrit value, serum E2 and progesterone levels were obviously declined [16]. Another study showed that 7-day administration of GnRH antagonist from the day of OPU significantly reduced serum E2 and effectively prevented the progression of mild to moderate and severe OHSS [17]. In the present study, we reviewed the data of 162 patients who underwent IVF/ISCI. We found that GnRH antagonist administration decreased 8% E2 level than that in the control group. Three-day administration of GnRH antagonist in the early luteal phase also resulted in an earlier onset of menses (an average of 3 days). It suggested that GnRH antagonist administration in the early luteal phase exerted a distinct luteolytic effect. There was no severe OHSS in the 82 patients who underwent GnRH antagonist

treatment, but 5 patients with severe OHSS were found in the control group and were all admitted into the hospital. Ultrasound examination on day 2 after OPU showed that the mean diameter of the bilateral ovaries was shorter in the antagonist group than in the control group. Administration of GnRH antagonist in the early luteal phase could prevent the progression of mild to moderate and severe OHSS.

OHSS is a result of ovarian over reaction during the follicular phase, which only occurs after the luteinizing hormone (LH) peak in the luteal phase or after HCG-triggered ovulation. OHSS enhances normal ovulation. IVF/ICSI simulation protocol usually leads to multiple mature follicles of each ovary. The release of vasoactive substances induced by HCG or LH results in OHSS. These vasoactive substances increased vascular permeability, third space fluid accumulation, hemoconcentration and hypovolemia [18]. Factors involved in OHSS consist of vascular endothelial growth factor (VEGF), prostaglandin, other components of cytokines family and endothelin-angiotensin system such as angiotensin II. All these factors have been confirmed to play a role in the normal physiological process of follicles and corpus luteum formation [19, 20]. The primary factor related to increased vascular permeability is VEGF, which is secreted by granular cells and theca cells during the late follicular phase. Vasculogenesis induced by VEGF is necessary for corpus luteum formation. It is believed that OHSS is the result of vascular permeability increase during revascularization induced by VEGF over-secretion. The level of free VEGF is correlated with the severity of OHSS. Inhibition of VEGF can improve vascular permeability [21, 22]. It has been reported that VEGF level in cultured luteal-phase granular cells decreased after GnRH antagonist treatment [23].

Conclusions

In conclusion, administration of GnRH antagonist in the early luteal phase during the process of IVF-ET can reduce the occurrence of OHSS, lower the incidence of moderate and severe OHSS and served as a safe and effective approach for OHSS. However, further studies are still required to uncover the exact mechanism of GnRH antagonist on OH.

Disclosure of conflict of interest

None.

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