Current Medical Science
DOI https://doi.org/10.1007/s11596-019-2031-5
39(2):278-284,2019

A Second Dose of GnRHa in Combination with Luteal GnRH Antagonist May Eliminate Ovarian Hyperstimulation Syndrome in Women with ≥30 Follicles Measuring ≥11 mm in Diameter on Trigger Day and/or Pre-trigger Peak Estradiol Exceeding 10 000 pg/mL*

Ling DENG[1†], Xue-lan LI[1, 2†], De-sheng YE[1], Christophe Blockeel[3], Xing-yu ZHOU[1], Shi-ling CHEN[1#], Xin CHEN[1#]
[1]*Center for Reproductive Medicine, Department of Gynecology and Obstetrics, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China*
[2]*Department of Reproductive Medicine, Jiangmen Central Hospital, Jiangmen 529030, China*
[3]*Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101-1090 Brussels, Belgium*

Summary: This observational study included 21 patients at remarkably high risk of ovarian hyperstimulation syndrome (OHSS), characterized by more than 30 follicles measuring ≥11 mm in diameter on trigger day and/or pre-trigger peak estradiol exceeding 10 000 pg/mL, which was also the feature of women with established severe early OHSS followed by gonadotrophin-releasing hormone agonist (GnRHa) trigger and freeze-all policy that previously have been reported. All patients received a second dose of GnRHa 12 h after the first GnRHa trigger combined with administration of GnRH antagonist at 0.25 mg/day for a period of 3 days from the day of oocyte retrieval onwards. The *in vitro* fertilization (IVF) outcomes may be preferable compared with a bolus of GnRHa trigger and none of the included patients developed moderate-to-severe OHSS. Moreover, patients' symptoms, reproductive hormone levels and ultrasound findings were improved significantly. This new strategy seems to be efficacious and could be a further supplement of GnRHa trigger with or without applying freeze-all strategy to completely prevent early-onset moderate to severe OHSS, especially for the patients characterized by ≥30 follicles measuring ≥11 mm in diameter on trigger day and/or pre-trigger peak estradiol exceeding 10 000 pg/mL. Further studies should be performed to compare this regimen with conventional methods of OHSS prevention.
Key words: *in-vitro* fertilization; ovarian hyperstimulation syndrome; GnRH agonist; GnRH antagonist; freeze-all

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of ovarian stimulation with an approximate incidence of moderate-to-severe OHSS ranging from 1% to 5% per cycle[1, 2]. Patients who develop OHSS should be carefully monitored as they may suffer from abdominal pain, nausea, vomiting, dyspnea, venous thrombosis, acute renal insufficiency and other life-threatening complications. There is even a mortality risk of OHSS, estimated to be 1 in 450 000 to 500 000 cases, which is low[3]. For this reason, over the years a lot of studies have focused on how to prevent and treat OHSS. The suggested strategies for mitigating the risk of OHSS include using gonadotrophin-releasing hormone (GnRH) antagonists, GnRH agonist (GnRHa) trigger, dopamine agonist administration and additional strategies such as use of metformin in polycystic ovary syndrome (PCOS) patients, calcium or aspirin administration, cryopreservation of embryos[4] and kisspeptin trigger[5].

In addition to its known inhibition activity of premature luteinizing hormone (LH) surge in the follicular phase, several studies reported that GnRH

Ling DENG, E-mail: dengling007@126.com; Xue-lan LI, E-mail: 752152188@qq.com
†These authors contributed equally to this work.
#Corresponding authors, Shi-ling CHEN, E-mail: chensl_92@163.com; Xin CHEN, E-mail: zhiduoxinrun@hotmail.com
*This work was supported by grants from the National Natural Science Foundation of China (No. 81401177) and Guangdong Province Natural Science Foundation (No. 2015A030313286), Milstein Medical Asian American Partnership Foundation Fellowship Award in Reproductive Medicine, Nanfang Hospital High-level Project Matching Funds (No. G2014005).

antagonist administration in luteal phase would induce luteolysis regardless of nature cycle or stimulation cycle with human choionic gonadotophin (hCG) inducing final oocyte maturation[6–8]. Furthermore, it has been described that luteal GnRH antagonist administration associated with a remarkable decline of serum vascular endothelial growth factor (VEGF) level[9], which is likely to be a significant factor of increment in vascular permeability that appears to be the pivotal mechanism for OHSS development[10, 11]. It presents a clue that the luteolytic effect of GnRH antagonist results in significant decline of VEGF thereby inducing regression of severe OHSS and preventing it from hospitalization[12–14]. Moreover, GnRH antagonist also can significantly decline the secretion of VEGF in granular luteinized cells by directly binding to the GnRHa receptor on those cells[15].

In order to completely avoid OHSS, a strategy that applies ovarian stimulation by performing GnRH antagonist protocol combined with GnRHa to trigger ovulation and then freezes all embryos has been proposed recently[16], and its efficacy was confirmed by subsequent studies[17, 18]. The use of a GnRHa trigger was initially advocated in the late 1980s and early 1990s[19, 20], with the induction of endogenous follicle-stimulating hormone (FSH) and LH surges similar to the natural cycle. Its successful induction of oocyte maturation was confirmed by our previous study[21], as well as other rigorous studies[22]. Although the short LH surge with around 18–24 h duration was sufficient to induce oocyte maturation, it was insufficient to support the development and function of the corpora luteum[23, 24], resulting in a decrease in the release of VEGF[25]. Thus, the use of a GnRHa trigger in efforts to prevent OHSS has become increasingly popular.

However, a number of severe OHSS cases have been reported in the high risk population even with a GnRH-agonist trigger and with applying a freeze-all strategy[26–31]. They all needed hospitalization and were treated with saline infusion or dopamine agonist or low molecular heparin or peritoneal drainage. Although it remains very difficult to understand how patients could develop OHSS following a GnRHa trigger, it normally causes a drastic luteolysis[32, 33]. Apparently, women in some rare cases did not successfully achieve luteolysis in a short time, since they menstruated as late as 12 days after oocyte retrieval (OR)[26]. Therefore, a single dose of GnRHa might be insufficient to cause luteolysis in women with high risk of moderate-to-severe OHSS and it is still necessary to further reduce the occurrence of OHSS.

Based on the above described evidence, we hypothesized that extending the duration of luteolysis by administering a second dose of GnRHa 12 h after the first, combined with the administration of GnRH antagonist during luteal phase might further enhance the luteolysis.

The following observational investigation was studied to explore the *in-vitro* fertilization (IVF) outcomes and the feasibility of this new regimen in patients who are at high risk of moderate-to-severe OHSS.

1 MATERIALS AND METHODS

1.1 Participants

This observational study included women aged 21–40 years at high risk of moderate-to-severe OHSS among 3718 IVF/intracytoplasmic sperm injection (ICSI) cycles from Center for Reproductive Medicine, Department of Gynecology and Obstetrics, Nanfang Hospital, Southern Medical University between January 2016 and June 2017.

All women who were treated with a second dose of GnRHa 12 h after the first and administration of GnRH antagonist at 0.25 mg/day for a period of 3 days from the day of OR onwards were enrolled in the study. Out of these patients, only those with ≥30 follicles measuring ≥11 mm in diameter on trigger day and/or a pre-trigger peak estradiol (E_2) exceeding 10 000 pg/mL in a GnRH antagonist cycle were included.

1.2 Treatment Protocols and Interventions

Patients were prescribed a flexible GnRH antagonist protocol and were stimulated with recombinant follicle-stimulating hormone (rFSH; Gonal F, Merck Serono, Italy) or highly purified FSH (HP-FSH; Lishenbao, Livzon Pharmaceuticals, China), starting on the second or third day of the cycle. Starting doses varied from 112.5 to 300 IU, based on the antral follicle count (AFC), female age, body mass index (BMI), and previous ovarian response. Gonadotropin doses were adjusted according to the individual response of the patient. As soon as one of the following criteria was reached: (i) the leading follicle reached a size of 14 mm, (ii) serum E_2 ≥600 pg/mL or (iii) serum LH level ≥10 IU/L; a GnRH antagonist (Cetrotide, Merck Serono, Germany) was administered at a dose of 0.25 mg/day until the day of trigger. When at least three follicles of ≥17 mm or two follicles measuring ≥18 mm in diameter were observed, final oocyte maturation was triggered with a first dose of GnRHa trigger (Triptorelin acetate, decapeptyl 0.2 mg, Ferring Pharmaceuticals, Israel) 35–36 h prior to OR, followed by a second dose of the GnRHa (Triptorelin 0.2 mg), 12 h after the first bolus.

Routine IVF and/or ICSI were performed, as appropriate. From the day of OR onwards, patients received a GnRH antagonist (Cetrotide 0.25 mg/day) for three consecutive days. All embryos were cryopreserved at the cleavage or blastocyst stage, which implies that a freeze-all policy was applied. Luteal support was not administered.

1.3 Follow-up

All patients were monitored from day 1 until day 3 after OR in order to assess the possibility of severe early-onset OHSS. Patients at high risk of moderate-to-severe OHSS underwent an ultrasound evaluation every day to assess ovarian size and ascites fluid. Ovarian size was calculated as maximal ovarian diameter. Blood tests including hematocrit (HCT) and white blood cell count (WBC), hepatic and renal function tests and measurement of serum E_2 and progesterone (P) were performed on day 1 and day 2 post-OR. Additionally, patients' clinical abnormalities such as abdominal distension, nausea, vomiting, dyspnea and other symptoms were monitored daily.

1.4 Criteria for the Diagnosis of OHSS

OHSS was diagnosed using previously published criteria[4]. Mild OHSS was diagnosed mainly by the presence of abdominal distension/discomfort, mild nausea/vomiting, mild dyspnea, diarrhea and enlarged ovaries. In addition to the above clinical features, once the ascites was presented by transvaginal ultrasound and a laboratory feature including hemoconcentration (HCT >41%) and elevated WBC (>15 000/mm^3) was measured, moderate OHSS was diagnosed. On the basis of mild and moderate features, severe OHSS was diagnosed when at least one of the following clinical criteria was reached: hydrothorax, clinical evidence of ascites, severe dyspnea, oliguria/anuria, intractable nausea/vomiting, severe hemoconcentration (HCT >55%), further elevated WBC (>25 000/mm^3) electrolyte disturbance (Na^+ <135 mEq/L or K^+ >5 mEq/L), abnormal renal function (creatinine >1.6 mg/dL, creatinine clearance <50 mL/min), or elevated liver enzymes.

The classification of ascites adopted in our unit was similar to previous published criteria[34, 35]. Low ascites was defined as a small amount of fluid that merely detectable by ultrasound in Douglas pouch; and moderate ascites was defined as an increased amount of ascitic fluid located in the small pelvis. When the fluid came up to the level of the umbilicus, the ascitic fluid was marked, and once significant accumulation of fluid was present, reaching the level of Morrison's pouch or the diaphragm, it was diagnosed as massive ascites or tense ascites, respectively.

1.5 Ultrasound and Laboratory Assays

Ultrasound measurements were performed using Aloka Prosound 6. The serum FSH, LH, E_2 and P concentrations were measured using electrochemiluminescence immunoassay [cobas e601, Roche Diagnostics (Shanghai) Ltd., China]. The inter-assay coefficients of variation (CV) for FSH, LH, E_2 and P were 4.5%, 2.2%, 4.9% and 4.8%, respectively. The intra-assay CV for FSH, LH, E_2 and P were 2.8%, 1.2%, 3.3% and 2.9%, respectively. WBC and hematocrit were determined by flow cytometry and impedance accumulation method, respectively. Serum albumin tests were checked by turbidimetric assay.

1.6 Statistical Methods

Statistical analysis was conducted using Statistical Product and Service Solutions (ver. 20.0; SPSS Inc., USA). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile ranges (IQR), depending on the distribution characteristics. The Paired-Sample *T* test was used when the continuous variables were normally distributed, otherwise the Wilcoxon Signed Ranks test was used. The Chi-Square (χ^2) test was used to compare categorical variables. The level of significance was set at 0.05.

1.7 Ethics

This study was approved by the ethics committee of Nanfang Hospital and written informed consent was obtained from each participant.

2 RESULTS

A total of 21 patients at high risk for moderate-to-severe OHSS who received the new regimen in IVF/ICSI cycle during those consecutive months were included in this study.

Baseline characteristics and hormone profiles of the 21 patients are shown in table 1. Ovarian stimulation parameters and IVF outcome are given in table 2. Totally, 61.90% (13/21) of patients' serum E_2 levels exceeded 10 000 pg/mL on the day of trigger, 52.38% (11/21) of patients had follicles measuring ≥11 mm in diameter on trigger day and in 66.67% (14/21) of patients, number of oocytes retrieved were more than 30, which indicated these patients were at remarkably high risk of severe early OHSS.

In terms of early-onset OHSS, there were 15 (71.43%) cases of mild OHSS and none of them did develop moderate-to-severe early OHSS. Moreover, none of the patients showed any signs of hydrothorax, dyspnea, oliguria or intractable nausea/vomiting

Table 1 Baseline characteristics and hormone profiles of the 21 patients

Items	Mean±SD, median (IQR) or percentage (*n*)
Age (years)	30.05±4.93
BMI (kg/m^2)	21.13±2.52
Duration of infertility (years)	4.29±3.05
First IVF/ICSI cycle	90.48% (19/21)
PCO/PCOS	95.24% (20/21)
AFC	29.80±8.30
Baseline FSH (mIU/mL)	5.82±1.48
Baseline LH (mIU/mL)	7.60±2.74
Baseline E_2 (pg/mL)	36.38 (15.45)
Baseline P (ng/mL)	0.53±0.18
Baseline T (ng/mL)	0.40±0.20

Table 2 Ovarian stimulation parameters and IVF/ICSI outcome

Parameters	IVF/ICSI outcome
Duration of stimulation (days)	9.00 (1.50)
Total Gn dose (IU)	1350.00 (637.50)
Follicles ≥ 11 mm in diameter	27.24±7.61
FSH at 12 h post-trigger (mIU/mL)	16.77±4.77
LH at 12 h post-trigger (mIU/mL)	57.49 (38.82)
E_2 at 12 h post-trigger (pg/mL)	10461.86±2545.06
P at 12 h post-triger (ng/mL)	11.31 (8.54)
Oocytes retrieved	32.57±8.91
Oocytes yield rate[a]	68.6% (684/997)
Top-quality embryos	5.00 (8.50)
Frozen embryos	6.00 (9.50)
Duration of luteal phase (days)	6.00 (2.00)

Continuous variable are presented as mean±SD or median (IQR); categorical variable showed as percentage (number).
[a:] Oocytes yield rate was defined as the ratio of the number of retrieved oocytes to the number of follicles punctured on the day of OR.

three days after OR. Outpatient observation was feasible for these patients, and none of them required hospitalization. Nineteen (90.48%) patients' menses started between 4 to 7 days after OR, while the other two patients' menses occurred as late as 13 days after OR.

As shown in table 3, no significant difference was observed between the mean level of serum E_2 on day 1 and day 2 post-OR. Compared to day 1 post-OR, a statistically significant reduction was observed in the concentration of serum P on day 2. There was one patient with WBC >15 000/mm^3 and two patients with HCT >41% on day 2 post-OR. Among them, 53.33% of patients' serum albumin was decreased slightly on day 2 post-OR.

A statistically significant difference in ovarian size was observed between the day of OR and day 1 post-OR. Ovarian size declined significantly (P<0.05) three days (day 3) after the initiation of GnRH antagonist administration, while no significant difference was observed in ovarian size between day 1 and day 2. None of the 21 patients were diagnosed with marked or massive ascites during the monitoring period. The proportion of moderate ascites was 42.86% (9/21) on day 1 post-OR, which significantly declined to 9.52% on day 3 (P<0.05).

3 DISCUSSION

This is, to our knowledge, the first study to investigate the strategy using two doses of GnRHa trigger in a GnRH antagonist cycle and GnRH antagonist administration for three days from the day of OR with the aim of mitigating the risk of early-onset moderate-to-severe OHSS.

Griesinger *et al*[29] showed that patients presented with ≥20 follicles ≥11 mm on the trigger day representing a true high-risk population for OHSS. So, for these patients, GnRHa trigger instead of hCG is suggested to induce final oocyte maturation for preventing OHSS, but there still existed 10 patients suffering from moderate to severe OHSS after GnRHa trigger without using hCG or embryos transfer[26–31], they were characterized by ≥30 follicles measuring ≥11 mm in diameter on trigger day and/or pre-trigger peak estradiol exceeding 10 000 pg/mL, and 7 of these patients retrieved more than 30 oocytes, which implies they were at drastically high risk of developing moderate-to-severe OHSS. All of the patients included in our study were equipped with at least one of the above characteristics and 66.67% (14/21) of patients' oocytes retrieved were more than 30, but none of them developed severe OHSS or needed hospitalization after applying this new strategy. Not only that, patients' symptoms, ultrasound and laboratory findings were improved after OR. This satisfactory outcome underlined that the new strategy would be efficacious and could be a further supplement of GnRHa trigger with or without applying freeze-all strategy to completely prevent early-onset moderate to severe OHSS.

Compared with our previous study[21], which used a bolus of GnRHa to induce final oocyte maturation, it is simple to understand that the LH levels at 12 h post-trigger followed by repeated doses of a GnRHa trigger were apparently higher than one bolus (46.60±23.20 mIU/mL). Additionally, the oocyte yield rate was remarkably higher in the present study and the number of top-quality embryos may be preferable. These might suggest that LH surge after triggering with a second dose of GnRHa 12 h after the first would be more conforming to the nature cycle, since it is well-demonstrated that the LH surge is characterized by three phases, lasting for 48 h in natural cycle, whereas the LH surge stimulated by one bolus of GnRHa just

Table 3 Variables associated with development of OHSS during early luteal phase (day 0, 1, 2, 3 following OR)

Variables	*n*	Day 0	Day 1	Day 2	Day 3
E_2 after OR	7	–	241.24±91.18	261.70±98.91	–
P after OR	7	–	56.80 (21.57)	28.50 (18.48)*	–
MOD (mm)	14	71.29±7.81**	76.43±7.07	81.71±10.06	74.07±5.82**
Moderate ascites	21	–	42.90% (9/21)		9.50% (2/21)*

Continuous variables are presented as mean±SD or median (IQR); categorical variable is shown as percentage (number). Asterisks represent statistically significant difference compared to day 2 ($^*P$<0.05, $^{**}P$<0.01).

consists of two phases, lasting for 24 h.

Consistent with Zelinski-Wooten' s study[36], our previous study (NCT number: NCT02022241) also proved that repeated doses of a GnRHa trigger could extend the duration of a LH peak, but it was still insufficient to maintain a normal luteal phase. Moreover, we found that this approach could effectively prevent the occurrence of moderate-to-severe OHSS. So, we hypothesized that this was owing to the extended luteolysis induced by the repeated doses of a GnRHa trigger. In our study, a clinical luteal-phase defect was observed in many patients who received two doses of a GnRHa trigger, as 90.48% of their duration of the luteal phase was between 4 to 7 days and the median (IQR) was 6.00 (2.00) days, which was consistent with previous studies[32, 33]. Although two patients' menses started as late as 13 days after OR, it is possible that there was an activating GnRH receptor mutation in these patients, as well as the possible involvement of an activating LH receptor and/or FSH receptor mutations[26].

Previously, the administration of GnRH antagonist was re-initiated during luteal phase in patients with established severe early OHSS which was induced by hCG trigger[7, 12], but in the present study, luteal GnRH antagonist was administrated in women who were still at high risk of moderate-to-severe OHSS after GnRHa trigger. We found the serum P levels, ovarian size and ascites were significantly declined with the administration of GnRH antagonist after GnRHa trigger. It implied that luteal GnRH antagonist could further suppress the development of OHSS in IVF/ICSI cycle after GnRHa trigger.

Lainas *et al*[7] reported that patients' ovarian volume, ascites, HCT, E_2 and P concentrations significantly declined as early as two days after the administration of GnRH antagonist, suggesting a rapid regression of severe OHSS. Although the same as Lainas's study, parameters including P levels, ovarian sizes as well as ascites also remarkably decreased in our study, they still slightly differ from Lainas's results. In the present study, on day 1 and 2, patients' ovarian size had increased instead of declining, and it started to decline only three days (day 3) following the initiation of GnRH antagonist administration. In addition to the ovarian size, after two days of GnRH antagonist administration, the serum E_2 levels also stayed the same and even slightly increased, which resembled the study of Kol *et al*[37], in which E_2 levels also remained unchanged on days 2 and 3 after OR in IVF/ICSI cycles with GnRHa trigger followed by no luteal GnRH antagonist and no luteal support. So, GnRH antagonist may exert effects on suppression of OHSS after three days of administration in our study population.

We speculated that these differences were because Lainas's study performed the GnRH antagonist administration on day 5. OHSS is recognized as a self-limited disease, usually regressing spontaneously over 10 to 14 days and resolving itself by the time of the next menstrual period[4, 38], so, the rapid resolution of ovaries in their study might stem from natural course of the syndrome, and not solely from the action of the GnRH antagonist. Furthermore, the patients in our study with ≥30 follicles measuring ≥11 mm in diameter on trigger day and/or pre-trigger peak E_2 exceeding 10 000 pg/mL, and moreover, from 66.67% (14/21) of whom more than 30 oocytes were collected, may probably develop moderate-to-severe OHSS, just like the patients presented in the above published studies[7, 26–31], yet no early severe OHSS occurred. This can likely be attributed to the use of two doses of a GnRHa trigger and the fact that we performed the GnRH antagonist administration at an earlier stage. Moreover, we suggest that at least three consecutive days of GnRH antagonist administration are needed for prevention and regression of OHSS but it still needs further investigation to determine.

To date, some clinical studies have suggested that luteal phase GnRH antagonist administration was safe and would not compromise the chance of a favorable pregnancy outcome, but the sample size was very small so the current results needed to be confirmed by larger trials[39, 40]. However, Siler-Khodr *et al*[41] reported that GnRH antagonist could greatly suppress the release of hCG, oestrone or oestradiol in the placental cultures, and GnRH antagonist administration in the early post-implantation period or early pregnancy would lead to adverse pregnancy outcomes such as abortion and low birth weight in rat and gilt[42, 43]. Moreover, it has reached a consensus that, without standard luteal phase support, pregnancy rates would be lower with a GnRHa trigger[6, 44]. So, more intense luteal supplementation and monitoring were needed if planning fresh embryo transfer after GnRHa trigger[45]. In summary, it remains a concern whether two doses of a GnRHa trigger and luteal GnRH antagonist administration would cause adverse effects on the outcomes of a fresh embryo transfer. However, with a freeze-all strategy, the above worries would be eliminated and the risk of late onset of OHSS would be avoided, so we suggested that the patients have all their embryos cryopreserved with this regimen.

Since our study was an observational study, one of the limitations in the present study was the lack of control groups. Therefore, we cannot precisely determine which one could exert a better effect on prevention of early-onset moderate-to-severe OHSS in the new strategy, the repeated dose of a GnRHa trigger or the GnRH antagonist administration on early luteal phase. Thus, further prospective controlled studies should be performed to compare this regimen with conventional methods of OHSS prevention.

In conclusion, our study showed that the regimen involving a second dose of GnRHa 12 h after the first and administration of GnRH antagonist at 0.25 mg/day for a period of three days from the day of OR, followed by a freeze-all strategy is an effective method to eliminate OHSS in women with ≥30 follicles measuring ≥11 mm in diameter on trigger day and/or pre-trigger peak E_2 exceeding 10 000 pg/mL. Furthermore, this regimen assisted in the regression of patients' symptoms, ultrasounds and laboratory findings.

Acknowledgements

The authors are grateful to the participating women as well as all the doctors, nurses and laboratory staff at the Center for Reproductive Medicine, Department of Gynecology and Obstetrics, Nanfang Hospital for their technical support and valuable suggestions.

Conflict of Interest Statement

The authors declare that there were no conflicts of interests regarding the publication of this article.

REFERENCES

1 Kawwass JF, Kissin DM, Kulkarni AD, *et al*. Safety of assisted reproductive technology in the United States, 2000-2011. JAMA, 2015,313(1):88-90
2 Steward RG, Lan L, Shah AA, *et al*. Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles. Fertil Steril, 2014,101(4):967-973
3 Brinsden PR, Wada I, Tan SL, *et al*. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. Br J Obstet Gynaecol, 1995,102(10):767-772
4 Pfeifer S BSDD. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril, 2016,106(7):1634-1647
5 Abbara A, Clarke S, Islam R, *et al*. A second dose of kisspeptin-54 improves oocyte maturation in women at high risk of ovarian hyperstimulation syndrome: a Phase 2 randomized controlled trial. Hum Reprod, 2017,32(9):1915-1924
6 Humaidan P, Bungum L, Bungum M, *et al*. Reproductive outcome using a GnRH antagonist (cetrorelix) for luteolysis and follicular synchronization in poor responder IVF/ICSI patients treated with a flexible GnRH antagonist protocol. Reprod Biomed Online, 2005,11(6):679-684
7 Lainas GT, Kolibianakis EM, Sfontouris IA, *et al*. Outpatient management of severe early OHSS by administration of GnRH antagonist in the luteal phase: an observational cohort study. Reprod Biol Endocrin, 2012,10:69
8 Mais V, Kazer RR, Cetel NS, *et al*. The dependency of folliculogenesis and corpus luteum function on pulsatile gonadotropin secretion in cycling women using a gonadotropin-releasing hormone antagonist as a probe. J Clin Endocrinol Metab, 1986,62(6):1250-1255
9 Lainas GT, Kolibianakis EM, Sfontouris IA, *et al*. Serum vascular endothelial growth factor levels following luteal gonadotrophin-releasing hormone antagonist administration in women with severe early ovarian hyperstimulation syndrome. BJOG, 2014,121(7):848-855
10 Krasnow JS, Berga SL, Guzick DS, *et al*. Vascular permeability factor and vascular endothelial growth factor in ovarian hyperstimulation syndrome: a preliminary report. Fertil Steril, 1996,65(3):552-555
11 Soares SR, Gomez R, Simon C, *et al*. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update, 2008,14(4):321-333
12 Bonilla-Musoles FM, Raga F, Castillo JC, *et al*. High doses of GnRH antagonists are efficient in the management of severe ovarian hyperstimulation syndrome. Clin Exp Obstet Gynecol, 2009,36(2):78-81
13 Lainas TG, Sfontouris IA, Zorzovilis IZ, *et al*. Management of severe OHSS using GnRH antagonist and blastocyst cryopreservation in PCOS patients treated with long protocol. Reprod Biomed Online, 2009,18(1):15-20
14 Lainas TG, Sfontouris IA, Zorzovilis IZ, *et al*. Management of severe early ovarian hyperstimulation syndrome by re-initiation of GnRH antagonist. Reprod Biomed Online, 2007,15(4):408-412
15 Asimakopoulos B, Nikolettos N, Nehls B, *et al*. Gonadotropin-releasing hormone antagonists do not influence the secretion of steroid hormones but affect the secretion of vascular endothelial growth factor from human granulosa luteinized cell cultures. Fertil Steril, 2006,86(3):636-641
16 Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. Hum Reprod, 2011,26(10):2593-2597
17 Atkinson P, Koch J, Ledger WL. GnRH agonist trigger and a freeze-all strategy to prevent ovarian hyperstimulation syndrome: A retrospective study of OHSS risk and pregnancy rates. Au N Z J Obstet Gynaecol, 2014,54(6):581-585
18 Karacan M, Erdem E, Usta A, *et al*. Gonadotropin-releasing hormone agonist triggering with concomitant administration of low doses of human chorionic gonadotropin or a freeze-all strategy in high responders. Saudi Med J, 2017,38(6):586-591
19 Itskovitz J, Boldes R, Levron J, *et al*. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. Fertil Steril, 1991,56(2):213-220
20 Lanzone A, Fulghesu AM, Apa R, *et al*. LH surge induction by GnRH agonist at the time of ovulation. Gynecol Endocrinol, 1989,3(3):213-220
21 Chen SL, Ye DS, Chen X, *et al*. Circulating luteinizing hormone level after triggering oocyte maturation with GnRH agonist may predict oocyte yield in flexible GnRH antagonist protocol. Hum Reprod, 2012,27(5):1351-1356
22 Youssef MA, Van der Veen F, Al-Inany HG, *et al*. Gonadotropin-releasing hormone agonist *versus* HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database Syst Rev, 201410): D8046
23 Chandrasekher YA, Brenner RM, Molskness TA, *et al*.

Titrating luteinizing hormone surge requirements for ovulatory changes in primate follicles. II. Progesterone receptor expression in luteinizinggranulosa cells. J Clin Endocrinol Metab, 1991,73(3):584-589
24 Zelinski-Wooten MB, Lanzendorf SE, Wolf DP, *et al*. Titrating luteinizing hormone surge requirements for ovulatory changes in primate follicles. I. Oocyte maturation and corpus luteum function. J Clin Endocrinol Metab, 1991,73(3):577-583
25 Cerrillo M, Pacheco A, Rodríguez S, *et al*. Effect of GnRH agonist and hCG treatment on VEGF, angiopoietin-2, and VE-cadherin: trying to explain the link to ovarian hyperstimulation syndrome. Fertil Steril, 2011,95(8):2517-2519
26 Fatemi HM, Popovic-Todorovic B, Humaidan P, *et al*. Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and “freeze-all” approach in GnRH antagonist protocol. Fertil Steril, 2014,101(4):1008-1011
27 Gurbuz AS, Gode F, Ozcimen N, *et al*. Gonadotrophin-releasing hormone agonist trigger and freeze-all strategy does not prevent severe ovarian hyperstimulation syndrome: a report of three cases. Reprod Biomed Online, 2014,29(5):541-544
28 Mahajan N, Gupta S, Sharma S, *et al*. Early onset ovarian hyperstimulation syndrome despite use of segmentation approach and ovarian hyperstimulation syndrome prophylaxis. J Hum Reprod Sci, 2015,8(4):234-238
29 Griesinger G, Schultz L, Bauer T, *et al*. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a "freeze-all" strategy: a prospective multicentric study. Fertil Steril, 2011,95(6):2029-2033, 2031-2033
30 Ling LP, Phoon JW, Lau MS, *et al*. GnRH agonist trigger and ovarian hyperstimulation syndrome: relook at 'freeze-all strategy'. Reprod Biomed Online, 2014,29(3):392-394
31 Santos-Ribeiro S, Polyzos NP, Stouffs K, *et al*. Ovarian hyperstimulation syndrome after gonadotropin-releasing hormone agonist triggering and "freeze-all": in-depth analysis of genetic predisposition. J Assist Reprod Genet, 2015,32(7):1063-1068
32 Hernández ER, Gómez-Palomares JL, Ricciarelli E. No room for cancellation, coasting, or ovarian hyperstimulation syndrome in oocyte donation cycles. Fertil Steril, 2009,91(4):1358-1361
33 Acevedo B, Gomez-Palomares JL, Ricciarelli E, *et al*. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. Fertil Steril, 2006,86(6):1682-1687
34 Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril, 2010,94(2):389-400
35 Pau E, Alonso-Muriel I, Gomez R, *et al*. Plasma levels of soluble vascular endothelial growth factor receptor-1 may determine the onset of early and late ovarian hyperstimulation syndrome. Hum Reprod, 2006,21(6):1453-1460
36 Zelinski-Wooten MB, Hutchison JS, Chandrasekher YA, *et al*. Administration of human luteinizing hormone (hLH) to macaques after follicular development: further titration of LH surge requirements for ovulatory changes in primate follicles. J Clin Endocrinol Metab, 1992,75(2):502-507
37 Kol S, Breyzman T, Segal L, *et al*. 'Luteal coasting' after GnRH agonist trigger - individualized, HCG-based, progesterone-free luteal support in 'high responders': a case series. Reprod Biomed Online, 2015,31(6):747-751
38 Whelan JR, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril, 2000,73(5):883-896
39 Eftekhar M, Miraj S, Mortazavifar Z. The effect of luteal phase gonadotropin-releasing hormone antagonist administration on IVF outcomes in women at risk of OHSS. Int J Reprod Biomed (Yazd), 2016,14(8):507-510
40 Lainas GT, Kolibianakis EM, Sfontouris IA, *et al*. Pregnancy and neonatal outcomes following luteal GnRH antagonist administration in patients with severe early OHSS. Hum Reprod, 2013,28(7):1929-1942
41 Siler-Khodr TM, Khodr GS, Rhode J, *et al*. Gestational age-related inhibition of placental hCG, alpha hCG and steroid hormone release in vitro by a GnRH antagonist. Placenta, 1987,8(1):1-14
42 Tug N, Uslu U, Cumbul A, *et al*. Effects of the gonadotropin-releasing hormone antagonist cetrorelix in the early postimplantation period on rat pregnancy. Eur J Obstet Gynecol Reprod Biol, 2011,155(2):166-170
43 Virolainen JV, Love RJ, Tast A, *et al*. Effect of a gonadotrophin-releasing hormone antagonist on luteinising hormone secretion and early pregnancy in gilts. Reprod Fertil Dev, 2003,15(7-8):451-459
44 Kolibianakis EM, Schultze-Mosgau A, Schroer A, *et al*. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. Hum Reprod, 2005,20(10):2887-2892
45 Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online, 2016,32(3):274-285

(Received July 30, 2018; revised Oct. 22, 2018)