Gonadotropin releasing hormone (GnRH) antagonist administration to decrease the risk of ovarian hyperstimulation syndrome in GnRH agonist cycles triggered with human chorionic gonadotropin

Ginevra Mills1 · Michael H. Dahan1

Received: 29 May 2022 / Accepted: 18 July 2022 / Published online: 6 August 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Purpose In Gonadotropin releasing hormone (GnRH) agonist IVF, after administration of human chorionic gonadotropin (hCG) triggering, there is a risk of ovarian hyperstimulation syndrome (OHSS). Few methods exist to prevent OHSS in these cases. Therefore, we investigated the use of a GnRH antagonist to decrease the risk of OHSS, due to its ability to decrease VEGF production and function.

Method A retrospective cohort study of 171-IVF patients at risk for developing OHSS after a GnRH agonist cycle with hCG trigger was performed from 2011 to 2019. The patient population consisted of women with an unexpected exuberant response to stimulation based on ovarian reserve testing and were triggered with hCG. Women were converted to a freeze-all cycle and received either cabergoline 0.5 mg orally alone for 7 days from the collection (Group 1, n = 123) or received cabergoline 0.5 mg orally and ganirelix, 250 mcg SC for 7–10 days (Group 2, n = 48).

Results Group 1 had more cases of moderate and severe OHSS than group 2 (25% vs. 10% p = 0.03, and 52% vs. 25% p = 0.001 respectively). Group 1 reported more abdominal discomfort and bloating than group 2 (91% vs. 65% p < 0.001) and the presence of free fluid was more frequent in group 1 than group 2 (74% vs. 35% p < 0.001). Hemoconcentration and electrolyte disturbances were less severe in group 2 than in group 1 (p < 0.001 all cases).

Conclusion In patients at high risk for developing OHSS after hCG trigger in a GnRH agonist cycle, the addition of GnRH antagonists in the luteal phase may reduce the risk of developing moderate and severe OHSS. The GnRH antagonist likely leads to more rapid luteolysis and down regulation of VEGF production and receptor response, thereby decreasing the hallmark increased vascular permeability.

Keywords GnRH antagonist · Cabergoline · IVF · OHSS · Ovarian hyperstimulation syndrome

What does this study add to the clinical work
GnRH antagonists can be used to prevent OHSS even in women triggered with hCG in long GnRH agonist protocols.
The GnRH antagonists likely work through a negative effect on VEGF production.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening iatrogenic disease associated with assisted reproductive technologies (ART) [1]. Current evidence suggests that OHSS remains an issue in IVF
cycles [2], despite prevention strategies. Active prevention of OHSS has become the gold standard of practice in ART and as a result, there has been a substantial decrease in the incidence of clinically significant OHSS [3]. The most effective method for reducing the risk of developing OHSS in patients at risk is to induce final oocyte maturation with a GnRH agonist rather than traditional oocyte maturation with human chorionic gonadotropin (hCG) in a GnRH antagonist cycle [4–7] combined with a freeze all strategy for the embryos. Unfortunately, the clinical decision to switch to a GnRH agonist trigger is only applicable when an antagonist ovarian stimulation protocol is used.

In GnRH agonist ART cycles, secondary risk reduction strategies can be employed. The main secondary OHSS risk reduction strategies are to cancel the cycle, or trigger with hCG and avoid fresh embryo transfer and administration of a dopamine agonist [8]. Cabergoline (a dopamine agonist) works by inhibiting both VEGF production and VEGF receptor phosphorylation, thereby reducing vascular permeability in women at risk for OHSS [9–12].

More recently, GnRH antagonists have been administered during the luteal phase of women with signs of OHSS to successfully enhance luteolysis, suppress ovarian enlargement, and inhibit the expression of VEGF from granulosa cells [13]. This intervention, either administered alone or in combination with cabergoline, after oocyte maturation with a GnRH agonist has been shown to successfully reduce vascular permeability and the development of moderate and severe OHSS [14]. However, up until now this strategy has only been used in combination with a GnRH-antagonist cycle triggered with a GnRH agonist, with the exception of several case reports.

In 2009, Rollene et al. published a case series of four patients diagnosed with OHSS on the day of retrieval of a GnRH agonist cycle that were treated with cabergoline 0.5 mg for 7 days along with ganirelix 0.25 mg daily for 2 days post retrieval. Patient symptoms of OHSS resolved within 5 days with no reported side effects [15]. In the same year, Lianas et al. also published a case report and article describing the use of GnRH antagonist in the luteal phase of three patients who developed OHSS 6 days after HCG trigger in a long agonist protocol [16, 17]. The patients in this study showed rapid improvement in their OHSS symptoms once the GnRH antagonist was started, and they went on to achieve live births. More recently, Zeng et al. published a study assessing the administration of a GnRH antagonist for 3 days, from days 3 to 5 post-oocyte retrieval, in women who displayed ultrasonographic evidence of moderate and severe OHSS at the time of oocyte retrieval. This study, which included both antagonist and agonist stimulation cycles, concluded that the luteal administration of GnRH antagonist can attenuate the symptoms of early significant OHSS and possibly attenuate its progression into a more severe form [18]. The results of these studies show promising results with the administration of GnRH antagonist with the appearance of OHSS signs at the time of oocyte retrieval.

Despite the extensive use of GnRH antagonists in ART cycles, there is currently limited data regarding the use of GnRH agonists in the early luteal phase, particularly in GnRH agonist cycles triggered with hCG [19]. There has yet to be a study conducted to examine the effects of continuous GnRH antagonist administration beginning on the day of oocyte retrieval in women identified as being at increased risk of developing OHSS after a GnRH agonist treatment cycle. The aim of this study, therefore, was to examine whether adding a GnRH antagonist to cabergoline treatment during the luteal phase after HCG trigger in GnRH agonist cycles with significant ovarian stimulation reduced the rate of OHSS when compared to treatment with cabergoline alone.

Materials and methods

This is a retrospective cohort study of 171 patients who underwent IVF treatment at the McGill University Health Centre from 2011 to 2019. Inclusion criteria were undergoing a GnRH agonist cycle with HCG trigger and subsequent conversion to a freeze all cycle based on high estradiol (E2) greater than 10,000 pmol/L or 17 or more oocytes collected. In many cases, GnRH-agonist cycles were planned for ovarian reserve testing suggesting borderline decreased ovarian reserve (in retrospect, in error). These results included low borderline serum AMH levels based on the assay used, antral follicle counts less than 12 or serum basal FSH levels greater than 12 IU/L. In several cases GnRH-agonist cycles were ordered due to patient allergies to GnRH-agonists. Some patients also received GnRH agonist cycles before all good responders were managed with GnRH antagonist cycles early on in the study period. (We were not completely aware of the benefit of GnRH antagonist cycles in preventing OHSS risk, particularly when combined with GnRH agonist trigger in 2011).

Exclusion criteria included use of a GnRH-antagonist cycle, stimulation of less than 17 oocytes and serum estradiol levels less than 10,000 pmol/L, failure to receive cabergoline post oocyte retrieval, use of aspirin or metformin from 30 days prior to 10 days post oocyte collection, cooling, and fresh embryo transfer.

Stimulation protocol Initial doses of gonadotropin were individualized for each patient according to age, basal follicle stimulating hormone (FSH) levels, antral follicle count (AFC), body mass index (BMI) and any previous responses to ovarian stimulation. Dose adjustments throughout the
cycle were performed according to ovarian response, as monitored by transvaginal ultrasonography and E2 levels. Subjects were treated with either the long GnRH agonist cycle or the GnRH-agonist microdose flare. In each case patient were treated with buserelin acetate (Superfact®, Sanofi-Aventis, Laval, Canada) subcutaneous injections (long GnRH agonist; buserelin 50 IU daily x 13 days with an oral contraceptive pill overlap (Marvelon, Merck, Canada), then 20 IU daily (with start of gonadotropins) until oocyte collection, microdose flare; buserelin 5 IU twice daily from cycle day 2 until oocyte collection). For more information on the protocols used, please see our previous publication [20]. In both cases, oral contraceptive pill pre-treatment was performed. Patients underwent ovarian stimulation by one of four possible methods: recombinant FSH (rFSH) alone (Gonal-F®, Merck-Serono, Toronto, Canada; or Puregon®, MSD) or in combination with recombinant LH (Luvaris Merck-Serono, Toronto Canada); human menopausal gonadotrophin (HMG) alone (Repronex or Menopur®, Ferring Pharmaceutical); or rFSH combined with HMG. All treatments were conducted as previously described [21]. Serum estradiol (E2) concentrations were routinely measured during stimulation cycle. All patients were triggered with either hCG 5000 IU or choriogonadotropin alpha (Ovidrel) (Merck-Serono, Toronto, Canada) 250 mcg via subcutaneous injection 36 h before oocyte retrieval. Women with an unexpected exuberant response to stimulation and/or more oocytes than measured follicles on the day of oocyte collection and converted to a freeze all cycle, were selected.

Study groups All the patients were allocated to one of two study groups. The first group received the standard cabergoline treatment (Dostinex® 0.5 mg, Pfizer, Montreal, Canada) 0.5 mg daily, orally for 7 days from the day of oocyte retrieval (Group 1, n = 123). The second group received the same cabergoline treatment for 7 days from oocyte retrieval in combination with a GnRH antagonist (ganirelix, Orgalutran® 0.25 mg/0.5 ml, Merck, Canada) subcutaneous for 7 days starting on the oocyte retrieval day continued the GnRH antagonist for 10 days if moderate or severe OHSS with free fluid occurred (Group 2, n = 48). All patients underwent vitrification of all high-quality blastocysts. No fresh embryo transfers were performed.

During the study period, five attending physicians were working at the fertility center. One physician gave the GnRH-antagonist and cabergoline to any subjects he collected who were at risk for OHSS, while the other four physicians gave Cabergoline alone. Each physician covered one operating room weekly and weekends were alternated. During coverage, the responsible physician in the operating room performed the oocyte collection for his and the other physicians patients, and decided on subsequent care for these subjects.

Patients returned 2–5 days after oocyte retrieval for evaluation of the presence of or complaints of symptomatology, sonographic examination of intraperitoneal free fluid and ovarian diameter measurements, and OHSS serum laboratory evaluations. This laboratory evaluation included a haemoglobin concentration, platelet count, serum sodium, potassium, albumin, liver function testing and coagulation levels. Coagulation levels included a prothrombin time, partial thromboplastin time and fibrinogen concentration as well as international normalized ratio. OHSS severity was determined according to the definition of Navot et al. (1992b).

Statistical analysis

Statistical evaluation was performed with independent sample t tests and chi-squared testing where appropriate. Continuous data were confirmed for normalcy using the Kolmogorov–Smirnov test. Data are presented as means and standard deviations or percentage depending if it was continuous or categorical data, respectively. Stepwise multivariate logistic regression analysis was performed controlling for age, serum FSH level, antral follicle count, and gonadotropin dose. Adjusted 95% confidence intervals are provided.

Ethical approval was obtained through the Institutional Review Board and the Institutional Ethics Committee of the McGill University Health Centre. Registration number: 2019-5129.

Results

A total of 171 patients undergoing IVF agonist and microdose flare cycles were identified as being at risk for developing OHSS after receiving an hCG trigger. (154 patients were treated with the long agonist protocol and 17 with the microdose flare protocol). All the patients were converted to a freeze-all cycle and were given cabergoline 0.5 mg PO for 7 days; 123 patients did not receive any other treatment (group 1) (Group 1 consisted of 12 subjects who had the microdose flare protocol and 111 who underwent the long GnRH-agonist protocol); 48 patients were simultaneously treated with cabergoline and a GnRH antagonist (5 who underwent the microdose flare protocol and 43 who underwent the long GnRH-agonist protocol). The demographics of these two groups are presented in Table 1. There were no significant differences found between the two groups in terms of age or ovarian reserve parameters. Outcomes of the ovarian stimulation (Table 2) were comparable with regards to the number of follicles greater than 9 mm and peak serum estradiol levels at the time of triggering. However, in group 2 there were more oocytes collected (18.6 vs. 17.1 p = 0.03), more embryos at the 2PN stage (14.3 vs. 12.2 p < 0.001), and more frozen blastocysts (4.4 vs. 3.9 p = 0.04). It should be noted that this should have placed group two at greater risk of ovarian hyperstimulation development.
However, when comparing rates of moderate and severe OHSS, group 2 had less cases of both moderate (25% vs. 74% \( p = 0.001 \)) and severe (10% vs. 25% \( p = 0.03 \)) OHSS. The presence of free pelvic fluid was higher in group 1 (74% vs. 35% \( p < 0.001 \)), and group 1 patients also experienced more bloating and discomfort than patients in group 2 (91% vs. 65% \( p < 0.001 \)). There was a trend to fewer hospital admissions in group 2 (25% vs. 15% \( p = 0.13 \)); however, the number of peritoneal ascites drainages/cases of severe OHSS were lower in group 2 (1.2 vs. 0.4 \( p = 0.01 \)).

When comparing laboratory testing on day 2–5 after oocyte retrieval, group 2 had lower serum hemoglobin levels (14.2 g/dl vs. 15.1 g/dl \( p < 0.001 \)), higher serum albumin concentrations (29.4 g/L vs. 23.6 g/L \( p < 0.001 \)), higher serum sodium levels (132.9 mEq/L vs. 132.0 mEq/L \( p = 0.02 \)), and lower serum potassium levels (4.6 mEq/L vs. 5.2 mEq \( p < 0.001 \)). Coagulation testing and liver function testing did not differ when both groups were compared (data not shown).

Logistic regression analysis was performed controlling for age, serum FSH level, antral follicle count, and gonadotropin dose. This failed to change results. Adjusted 95% confidence intervals are provided in Table 3. After consultation with a statistician we elected not to control for stimulation outcomes including number of follicles, number of oocyte and embryos, since these were higher in the group with less OHSS outcomes (even though they were more at risk). Therefore, controlling for these factors would have been inappropriate to do.

**Discussion**

The aim of this study is to compare rates of moderate and severe OHSS among women with unexpectedly high ovarian stimulation in a GnRH agonist cycle and hCG trigger after treatment with cabergoline alone or in combination with a GnRH antagonist on the same day but after oocyte collection in a freeze-all cycle. To our knowledge, a comparison such as this has not been previously reported in the literature. Relative to cabergoline alone, treatment with cabergoline and a GnRH antagonist after oocyte collection in women at risk of developing OHSS significantly reduced the occurrence of moderate and severe OHSS. Addition of GnRH antagonist to the currently accepted treatment of cabergoline reduces the accumulation of free fluid in the pelvis and improves levels of patient discomfort and bloating. Furthermore, GnRH antagonist treatment resulted in improvements in serum blood electrolyte concentrations and prevented hemoconcentration, suggesting an improvement in mild OHSS symptomatology.

The GnRH agonist ovarian stimulation cycle is an important protocol for use in select patients undergoing ART who are either not candidates for an antagonist protocol, such as those with an allergy to GnRH antagonists, or those who have failed to respond well to an antagonist protocol in the past. The GnRH-agonist cycle may also be the preferred stimulation protocol for women with endometriosis, although this can be debated [22]. Finally, there are two prospective randomized trials comparing outcomes of stimulation protocols in poor responders. In one, the “long agonist protocol” and microdose flare with OCP (oral contraceptive) pre-treatment gave more MII oocytes when compared with the antagonist although not statistically significant [23]. In the other study, the long protocol gave more MII oocytes and embryos than did the antagonist (microdose OCP was not studied), although again not statistically more

### Table 1 Baseline data comparing those with and without use of GnRH antagonist

|                  | Group 1 Cabergoline alone (N=123) | Group 2 GnRH-antagonist + Cabergoline (N=48) | p value |
|------------------|-----------------------------------|---------------------------------------------|---------|
| Mean Age of Female (years)  | 36.2 ± 2.8 | 35.8 ± 3.2 | 0.42   |
| Serum basal FSH level (IU/L) | 8.1 ± 2.3 | 7.9 ± 2.3 | 0.61   |
| Serum basal estradiol levels (pmol/L) | 242 ± 27 | 250 ± 32 | 0.10   |
| Antral Follicle Count (n) * | 12.2 ± 2.4 | 11.6 ± 1.9 | 0.12   |
| PCOS diagnosis | 0% (0/123) | 0% (0/48) | NS     |

### Table 2 Stimulation parameters comparing those with and without use of GnRH antagonist

|                  | Group 1 Cabergoline alone (N=123) | Group 2 GnRH-antagonist + Cabergoline (N=48) | P value |
|------------------|-----------------------------------|---------------------------------------------|---------|
| All follicles at least 10 mm at triggering | 17.5 ± 4.4 | 17.8 ± 3.8 | 0.68   |
| Peak serum estradiol levels at triggering (pmol/L) | 11.387 ± 2092 | 12.001 ± 1898 | 0.08   |
| Oocytes Collected | 17.1 ± 3.8 | 18.6 ± 4.2 | 0.03   |
| 2PN Embryos      | 12.2 ± 2.9 | 14.3 ± 1.7 | 0.0001 |
| Frozen Blastocysts* | 3.9 ± 1.3 | 4.4 ± 1.7 | 0.04   |
Both of these studies included few subjects which may have impacted the power. However, based on these results there are arguments to use the long and the microdose (with OCP) GnRH-agonist cycles in anticipated poor responders. Currently, there is no recent data on the number of GnRH agonist cycles performed for these purposes. However, a study looking at IVF cycles from the Society for Assisted Reproductive Technology (SART) data between 2008 to 2011 inclusively demonstrated that more than 75,000 GnRH-agonist cycles were performed in that time period as compared to 50,000 GnRH antagonist cycles [25]. Although, the use of GnRH agonist trigger in GnRH-antagonist cycles and benefits as related to rates of OHSS were first described in 2000 by Itskovitz-Eldor et al. [7], and the first meta analysis on the subject to show promising effect of the treatment was published in 2006 [26], many patients continue to be treated with GnRH-antagonist cycles. Given that the GnRH-agonist protocols continue to be used, we would argue that the knowledge of these results are important to prevent unexpected OHSS in modern fertility care.

It is important to note that while there were no significant differences between the treatment groups with respect to their risk factors for developing OHSS at the time of hCG trigger (namely follicle number and peak serum E2 levels), group 2 was found to have a higher number of oocytes collected, a higher number of 2PN embryos, and a higher number of frozen blastocysts. This difference would lead one to suspect that group 2 would have a propensity towards higher rates of OHSS signs and symptoms. However, the opposite was found: group 2 had lower rates of moderate and severe OHSS, less peritoneal fluid accumulation, bloating and discomfort, and improved blood serum parameters. Therefore, one could postulate that the effects seen in this study are more clinically significant that they appear, given that the GnRH treatment group had better ART cycle outcomes with lower OHSS signs and symptoms. Clearly, the most at risk women were treated with the GnRH-antagonist yet demonstrated better results.

The question remains what is the mechanism of action of a GnRH antagonist decreasing the risk of OHSS in GnRH agonist cycles. Excessive stimulation of the granulosa cells via the FSH receptor in the follicular phase is known to increase the expression of CYP19AI enzyme (aromatase), leading to the rapid increase in estrogen production [27]. In GnRH agonist cycles with significantly elevated estradiol levels, agonist withdrawal before oocyte retrieval decreases the CYP19AI enzyme activity, which accounts for the leveling of estradiol levels [28] (Ding et al.). VEGF mRNA is also expressed in granulosa cells and concentrations of VEGF in follicular fluid are also found to be decreased with withholding of the GnRH agonist [28]. The addition of a GnRH antagonist would competitively inhibit the action of GnRH agonists and as such would be expected to have a similar effect. Indeed, when one to two doses of GnRN antagonists were administered prior to hCG ovulation trigger, risk of OHSS were decreased in a prospective randomized study [29].

GnRH antagonist administration has been shown to downregulate the expression of VEGF mRNA in human granulosa cells and simultaneously inhibit transcription
factors for the CYP19IIa and AMH expression [28, 30–32]. GnRH receptors are present in the lutenized granulosa cells at a greatly increased number compared to the granulosa cells of the follicular phase [32]. This increase in receptor number begins with the onset of ovulation induction, either by LH surge or hCG administration [33]. Therefore, one could postulate that decreasing GnRH receptor stimulation as early as ovulation induction or oocyte retrieval could play a role in reducing the risk of OHSS in women who are at high risk. When analyzing the differing effects of ovulation trigger on granulosa cells, there are lower levels of both VEGF and CYP19AI mRNA expression in the follicular fluid of women who receive the shorter lutenizing GnRH agonist trigger when compared to an hCG trigger [34]. These results support the notion that down-regulating granulosa cell GnRH receptor activation as early as possible after oocyte retrieval, as is done in this study, can severely attenuate the underlying physiological mechanism for the development of OHSS.

Despite the significant results of this study, it is not without its limitations. First, as a retrospective cohort study, there may be a certain amount of selection and misinformation bias that cannot be accounted for. Second, it has a moderate sample size, with only 48 patients in the intervention group, suggesting the possibility of a type 1 error. Given the levels of significance between group outcomes, however, this risk remains low. Conversely, this study’s strengths are three-fold: The intervention comprises a simple, well defined, and easily reproducible protocol, thereby increasing external validity. Internal validity is also enhanced based on the objective assessments of OHSS signs and symptoms. Finally, this is the first study to date comparing the effectiveness of a novel secondary OHSS prevention strategy with the already well-established protocol of stand-alone cabergoline treatment in the setting of a freeze-all cycle treated with the GnRH-agonist protocol.

**Conclusion**

In patients at high risk for developing OHSS after hCG trigger in a GnRH agonist cycle, the addition of GnRH antagonists in the luteal phase may reduce the risk of developing moderate and severe OHSS. When a GnRH antagonist is added to the standard therapy of cabergoline and no embryo transfer, it may diminish the effects of additional ovarian stimulation caused by administration of an hCG trigger. The GnRH antagonist likely leads to more rapid luteolysis and downregulation of VEGF production and receptor response, thereby decreasing the hallmark increased vascular permeability. As a result, there is decreased peritoneal fluid accumulation, more normalized serum biomarkers of OHSS, and reduced risk of catastrophic VTE events. Given the promising results of this study, further randomized control studies to better elucidate these findings would be appropriate.

**Author contributions** MHD, GM contributed to the study conception and design. Material preparation, data collection and analysis were performed by MHD, GM. The first draft of the manuscript was written by MHD and GM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Declarations**

**Conflict of interest** The authors have no conflicts of interest related to this article. No funding was available for this article.

**Ethics approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of McGill University Health Center # 2019–5129.

**Consent to participate** Being a retrospective study, an informed consent waiver was obtained from the director of professional services of the MUHC.

**Consent to publish** Being a retrospective study, consent to publish was obtained from the director of professional services of the MUHC.

**References**

1. Golan A et al (1989) Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv 44:430–440
2. Rotshenker-Olshinka K et al (2020) Trends in ovarian hyperstimulation syndrome hospitalization rates in the USA: an ongoing concern. Reprod Biomed Online 41:357–360
3. Papanikolaou EG et al (2006) Incidence and prediction of ovarian hyperstimulation syndrome after gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril 85:112–120
4. Corbett S et al (2014) The prevention of ovarian hyperstimulation syndrome. J Obstet Gynaecol Can 36:1024–1033
5. Fatemi HM et al (2014) Severe Ovarian Hyperstimulation Syndrome after Gonadotropin-Releasing Hormone (Gnrh) Agonist Trigger And “Freeze-All” Approach in Gnrh Antagonist Protocol. Fertil Steril 101:1008–1011
6. Mourad S, Brown J, Farquhar C (2017) Interventions for the prevention of Ohss in art cycles: an overview of cochrane reviews. Cochrane Database Syst Rev 1:CD012103
7. Itskovitz-Eldor J, Kol S, Mannaerts B (2000) Use of a Single Bolus of Gnhr Agonist Triptorelin to Trigger Ovulation after Gnrh Agonist Ganirelix Treatment in Women Undergoing Ovarian Stimulation for Assisted Reproduction, with Special Reference to the Prevention of Ovarian Hyperstimulation Syndrome: Preliminary Report. Hum Reprod 15:1965–1968
8. Alvarez C et al (2007) Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab 92:2931–2937
9. Tang H et al (2016) Dopamine agonists for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev 11:CD008605

10. Tsunoda T et al (2003) Treatment for ovarian hyperstimulation syndrome using an oral dopamine prodrug, Docarpamine. Gynecol Endocrinol 17:281–286

11. Carizza C et al (2008) Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study. Reprod Biomed Online 17:751–755

12. Manno M et al (2005) Cabergoline: a safe, easy, cheap, and effective drug for prevention/treatment of ovarian hyperstimulation syndrome? Eur J Obstet Gynecol Reprod Bio 122:127–128

13. Dahan MH, Tannus S, Seyhan A, Tan SL, Ata B (2018) Combined modalities for the prevention of ovarian hyperstimulation syndrome following an excessive response to stimulation. Gynecol Endocrinol 34:252–255

14. Shrem G et al (2019) Use of cabergoline and post-collection GnRH antagonist administration for prevention of ovarian hyperstimulation syndrome. Reprod Biomed Online 39:433–438

15. Rollene NL et al (2009) Treatment of ovarian hyperstimulation syndrome using a dopamine agonist and gonadotropin releasing hormone antagonist: a case series. Fertil Steril 92(1169):e15–e17

16. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E et al (2009) Live births after management of severe OHSS by GnRH antagonist administration in the luteal phase. Reprod Biomed Online 19:789–795

17. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Iliadis GS et al (2009) Management of severe OHSS using GnRH antagonist and blastocyst cryopreservation in Pcos patients treated with long protocol. Reprod Biomed Online 18:15–20

18. Zeng C et al (2019) The effect of luteal GnRH antagonist on moderate and severe early ovarian hyperstimulation syndrome during in vitro fertilization treatment: a prospective cohort study. Arch Gynecol Obstet 300:223–233

19. Lainas GT et al (2013) Pregnancy and neonatal outcomes following luteal GnRH antagonist administration in patients with severe early OHSS. Hum Reprod 28:1929–1942

20. Dahan MH et al (2014) A Comparison of Outcomes from in Vitro Fertilization Cycles Stimulated with Either Recombinant Luteinizing Hormone (Lh) or Human Chorionic Gonadotropin Acting as an Lh Analogue Delivered as Human Menopausal Gonadotropins, in Subjects with Good or Poor Ovarian Reserve: a retrospective analysis. Eur J Obstet Gynecol Reprod Biol 172:70–73

21. Rose BI (2014) Approaches to oocyte retrieval for advanced reproductive technology cycles planning to utilize in vitro maturation: a review of the many choices to be made. J Assist Reprod Genet 31:1409–1419

22. Drakopoulos P et al (2018) Does the type of GnRH analogue used, affect live birth rates in women with endometriosis undergoing IVF/ICSI treatment, according to the rafs stage? Gynecol Endocrinol 34:884–889

23. Dakhly DM, Bayoumi YA, Allah SHG (2016) Which Is the Best IVF/ICSI Protocol to Be Used in Poor Responders Receiving Growth Hormone as an Adjuvant Treatment? A Prospective Randomized Trial. Gynecol Endocrinol 32:116–119

24. Sunkara SK et al (2014) Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. Fertil Steril 101:147–153

25. Londra L et al (2016) Is the type of gonadotropin-releasing hormone suppression protocol for ovarian hyperstimulation associated with ectopic pregnancy in fresh autologous cycles for in vitro fertilization? Fertil Steril 106:666–672

26. Griesinger G (2006) GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. Reprod Biomed Online 13:628–638

27. Stocco C (2008) Aromatase expression in the ovary: hormonal and molecular regulation. Steroids 73:473–487

28. Ding LJ et al (2013) Withdrawal of GnRH agonist decreases oestradiol and VEGF concentrations in high responders. Reprod Biomed Online 27:131–139

29. Prapas Y et al (2017) GnRH Antagonist Administered Twice the Day before HCG Trigger Combined with a Step-Down Protocol May Prevent OHSS in IVF/ICSI Antagonist Cycles at Risk for OHSS without Affecting the Reproductive Outcomes: a prospective randomized control trial. J Assist Reprod Genet 34:1537–1545

30. Asimakopoulos B et al (2006) 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 86:636–641

31. Winkler N et al (2010) Gonadotropin releasing hormone antagonists suppress aromatase and anti-müllerian hormone expression in human granulosa cells. Fertil Steril 94:1832–1839

32. Lee A et al (1997) Vascular endothelial growth factor production by human luteinized granulosa cell cultures. Fertil Steril 106:666–672

33. Prapas Y et al (2017) GnRH Antagonist Administered Twice the Day before HCG Trigger Combined with a Step-Down Protocol May Prevent OHSS in IVF/ICSI Antagonist Cycles at Risk for OHSS without Affecting the Reproductive Outcomes: a prospective randomized control trial. J Assist Reprod Genet 34:1537–1545

34. Winkler N et al (2010) Gonadotropin releasing hormone antagonists suppress aromatase and anti-müllerian hormone expression in human granulosa cells. Fertil Steril 94:1832–1839

35. Lee A et al (1997) Vascular endothelial growth factor production by human luteinized granulosa cell cultures. Fertil Steril 106:666–672

36. Prapas Y et al (2017) GnRH Antagonist Administered Twice the Day before HCG Trigger Combined with a Step-Down Protocol May Prevent OHSS in IVF/ICSI Antagonist Cycles at Risk for OHSS without Affecting the Reproductive Outcomes: a prospective randomized control trial. J Assist Reprod Genet 34:1537–1545

37. Winkler N et al (2010) Gonadotropin releasing hormone antagonists suppress aromatase and anti-müllerian hormone expression in human granulosa cells. Fertil Steril 94:1832–1839

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.