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Full length article

Combining several interventions to reduce the incidence of OHSS: A prospective cohort study

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ABSTRACT

Objective: To assess the outcome of using low-dose aspirin, dopamine agonist and triggering ovulation by low dose of HCG in combination with GnRH agonist in fixed GnRH antagonist protocol in patients at risk of OHSS.

Study design: This prospective cohort study was conducted on 50 infertile women who were at high risk of OHSS. They received low dose aspirin from first day of stimulation, cabergoline 0.5 mg daily from the day of HCG for 8 days and low dose of HCG (2500 IU) in combination with GnRH agonist for final oocyte maturation in fixed GnRH antagonist protocol.

Results: The study was conducted on 50 cases and all of them completed the study protocol. The clinical pregnancy rate was 40% (20 cases of 50) and no cases developed severe or critical OHSS. Only 8% (4 cases) developed moderate OHSS.

Conclusion: Combining aspirin, cabergoline, and triggering with low dose of HCG in combination with GnRH agonist produced excellent clinical pregnancy rate, and decreased hospital admissions with severe or critical OHSS.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of controlled ovarian stimulation occurring during the luteal phase or early in pregnancy. Most cases are mild, but forms of moderate or severe OHSS appear in 3% to 8% of in vitro fertilization (IVF) cycles. OHSS is usually self-limited, but occasionally life threatening, characterized by ovarian enlargement caused by multiple follicular, theca lutein ovarian cysts and an acute fluid shift into the extravascular space due to increased capillary permeability. It is complicated with ascites, pleural effusion, hemoconcentration, hypovolemia, electrolyte imbalance, and thromboembolic manifestations [1,2].

Several different approaches have been taken to minimize the development of OHSS in IVF patients. The most common approach is to predict susceptible patients based on medical history; polycystic ovary syndrome (PCOS), past history of OHSS,ovarian reserve assessment by serum anti-Mullerian hormone (AMH) and antral follicle count (AFC) [3,4]. A high ovarian response (examined by the number of large follicles, estradiol concentration or the number of retrieved oocytes) is the best method of predicting the occurrence of OHSS. [5]. Initiate a lower dose of gonadotrophin stimulation to diminish the risk of an exaggerated response. Unfortunately this approach does not always prevent OHSS and may lead to an unexpected suboptimal low oocyte response [6]. Alternatively, if a patient develops an excessive response, gonadotrophin stimulation may be withdrawn for several days 'coasting' until the estrogen levels fall to a safer level before administering HCG [7]. The cryopreservation of all embryos is an effective treatment to prevent late-onset OHSS, but it is not popular with patients and does not avoid early-onset OHSS [8,9].

New pharmacological methods of minimizing OHSS severity have been shown to be of some benefit. Cabergoline was found to reduce the occurrence of moderate or severe OHSS without relevant negative impact on clinical pregnancy or on oocyte yield [5,10,11]. Low-dose aspirin therapy during ovulation induction also used for prevention of OHSS in high-risk patients [12,13].

GnRH agonist triggering is a valid alternative to HCG triggering, resulting in elimination of OHSS. Modified luteal phase support and adding low dose of HCG (1500 IU) to GnRH agonist improved pregnancy rate and reproductive outcome without increase in the incidence of OHSS [14–16].

The aim of this work was to study the effect of combining low-dose aspirin and cabergoline in GnRh antagonist protocol with low dose of gonadotrophin and triggering by GnRH agonist combined

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with low dose of HCG. Our rationale was to benefit from the effect of the combined regimen in lowering the incidence of severe OHSS and to benefit from the low dose of HCG in improving pregnancy outcome.

Materials and methods

Study design: prospective cohort study

Setting: This study was carried out in El-Shatby Maternity University Hospital. It was started in September 2014 till October 2015. Cases were recruited from the fertility clinic within the hospital and followed up during the time of study mentioned previously.

This study has been approved by national research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: "Informed consent was obtained from all individual participants included in the study."

participants: 50 patients scheduled for ICSI with risk for OHSS and with previous history of severe OHSS.

Eligibility criteria, include: women less than 30 years old, high antral follicle count (more than 20) [17] (for better selection of cases at high risk), BMI less than 30 kg/m^2 and cases with past history of severe OHSS. [18]

Exclusion criteria: Patients more than 30 years old, BMI more than 30 kg/m^2, patients with endometriosis and with history of medical diseases as hypothyroidism or uterine anomalies as septum were excluded.

Variables: The primary outcome was the incidence of severe or critical early ovarian hyper stimulation.

The secondary outcome was clinical pregnancy rate.

Data sources/measurement

1 OHSS was assessed according to the classification of:

Rizk et al. [18]

Moderate: Discomfort, pain, nausea, abdominal distension, US evidence of ascites and enlarged ovaries, normal hematological and biological profiles.

Severe: Grade A: Dyspnea, oliguria, nausea, vomiting, diarrhea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, US showing large ovaries, marked ascites and normal biochemical profile. Grade B: Grade A + massive tension ascites, markedly enlarged ovaries, severe dyspnea, marked oliguria, increased Hct, elevated serum creatinine and liver dysfunction. Grade C: Complications such as respiratory distress syndrome, renal shut-down or venous thromboembolism.

Lyons et al. [19]:

Early: OHSS occurring 3–7 days after HCG administration.

Late: OHSS occurring 12–17 days after HCG administration.

- Clinical pregnancy rate: the number of clinical pregnancies expressed per 100 initiated cycles. Pregnancy was detected by measuring serum HCG at least 15 days after embryo transfer. Clinical pregnancy was determined by observation of a gestational sac with fetal cardiac pulsations by transvaginal ultrasound at 6 weeks of pregnancy [20].

Bias: all the scheduled cases were enrolled in the same protocol.

Study size: 50 infertile cases completed the study without any cancellation.

Procedure: After complete history taking, examination, transvaginal ultrasound (TVUS), counseling for ICSI and hormonal investigations; basal FSH, LH, E2 and AMH were determined. ICSI was started through fixed antagonist protocol. 2 ampoules of HMG (150 IU/day I.M), were used from second day of cycle. Low-dose aspirin (Aspocid75 mg, one tablet per day) was administered from the first day of stimulation till 12 weeks or negative pregnancy test. Patients were evaluated at 6th day of stimulation to adjust the dose of HMG, and to start GnRH antagonist (Cetrotide, Serono 0.25 mg S. C) (fixed protocol). Serial follow up by every other day measurement of serum E2 level and TVUS till the day of triggering ovulation. Ovulation triggering was induced when most of the follicles exceeded 18 mm in diameter.

Cabergoline (Dostinex® PFIZER 0.5 mg; half tablet twice daily) starting from the day of ovulation triggering for 8 days.

Triggering of final oocytes maturation by using low dose of (2500 IU) HCG (Choriomon IBSA I.M) in combination with GnRH agonist (decapeptyle ®, Ferring 0.1 mg S.C). Oocyte retrieval was done 34–36 h after triggering under light sedation. 3–5 good quality embryos were selected and mounted in the transfer catheter and transferred transcervically guided by ultrasound in the appropriate time. Luteal phase was supported by (Prontogest Supp®, Marcyrl) 400 mg, twice daily vaginally in addition to (Prontogest® ampoule, Marcyrl) 100 mg, once daily I.M was continued until negative pregnancy test or until completion of first trimester. I.M progesterone can be stopped after confirmation of cardiac pulsations.

After ET serial assessment of hematocrite, WBCS, serum urea, creatinine, serum albumin, total proteins and serum electrolytes was done every other day.

Quantitative B-HCG was done 2 weeks after ET.

Statistical methods

Sample size calculation: A sample size of 45woman was the enough required sample to detect an expected proportion of 6% in the primary outcome (severe OHSS) [21,22], as statistically significant with 80% power and at a significance level of 0.05. Sample size per group increased to 50 to control attrition bias [23]. The sample size was calculated using G Power version 3.1.9.2 [24]. Results were confirmed by online calculator http://www.sample-size.net/sample-size-conf-interval-proportion/ [22]

Statistical analysis

Data was collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (ver 21) [25]. Data was entered as appropriate (numerical or categorical). When Kolmogorov-Smirnov test revealed no significance in the distribution of variables, parametric statistics was carried out [26]. Exploration of the data yielded complete descriptive statistics including (choose) the minimum and maximum of range, mean, and standard deviation or the minimum, maximum, range, mean and standard deviation. In the present study an alpha level was set to 5% with a significance level of 95% and an accepted beta error up to 20% with a power of study of 80%. Independent sample *t*-test was used for comparison of means between two independent groups.

Results

This study was initially done on 50 women scheduled for ICSI. Through the period of the study (13 months) there were no missing women either by cycle cancellation or withdrawal.

All patients were from the same region (Alexandria, Egypt). All patients were similar regards to the risk for severe OHSS. All the patients were followed up until the end of the treatment regimen by the two authors. There was no special exposure to any other risks such as medical illness in any one in the group.

Through the period of the study only 12 cases developed moderate OHSS as described by Rizk et al. [18]. There was only a significant difference in serum albumin between the OHSS and non OHSS groups (3.71 ± 0.41 g/L) versus (4.10 ± 0.33 g/L) but still within the physiological range. In previous attempts 7 of these cases showed history of severe OHSS and 5 of them were admitted to the ICU with the use of different single intervention such as low-dose aspirin, cabergoline, antagonist protocol or intravenous colloids infusion. 8 cases (66%) of this group (OHSS) developed biochemical pregnancy, 7 cases of them (58%) developed clinical pregnancy with one case of first trimester miscarriage.

The mean age of the patients was 27.24 ± 2.39 years. The mean body mass index and other basic data were shown in (Table 1). Clinical characteristics of the treatment cycle as regards maximum E2 level (pg/ml), Progesterone on HCG day (ng/ml), endometrial thickness on HCG day, number of ampoules and duration of stimulation (days) were shown in (Table 2).

Comparing the characteristics of the stimulation cycle between OHSS and non OHSS groups as regards basal hormonal level, days of stimulation, number of gonadotrophin ampoules and number of antagonist ampoules were shown in (Table 1)

Regarding OHSS development, 12 cases (24%) developed moderate OHSS while none developed severe or critical OHSS.

There were no statistical significant differences between non-OHSS and OHSS cases concerning WBCs, hematocrit, urea, and creatinine levels at day of HCG, OR, ET, and 7 days after ET. Serum albumin level was 4.10 ± 0.33 g/L in non-OHSS while in OHSS was 3.71 ± 0.41 g/L at day of OR. This difference was statistically significant but still both levels are within the physiological range.

24 cases (48%) experienced biochemical pregnancy, 20 cases (40%) got clinically pregnant, 10 cases (20%) conceived a singleton, 8 cases (16%) conceived twins, 2 cases conceived triplet and two cases experienced miscarriage. Table 6 shows that there was no significant difference between group of OHSS and non OHSS as regards number of mature oocytes, cleavage rate, number of embryos and class A embryos in the stimulation cycle.

Discussion

Though several approaches have been proposed to prevent the development of severe OHSS, the preventative strategies are not completely effective, as the pathophysiology of this condition is not clearly understood and factors predicting its occurrence have not been identified with confidence. In this study there were no cases of severe or critical OHSS after combining this multiple approaches in susceptible cases. Only 12 cases (24%) of moderate OHSS were developed without any hospital admissions.

The limitations for this study were the inability to show the efficacy of low-dose aspirin versus oral cabergoline in prevention of severe OHSS. In this study the combination was selected of cases were at extreme risk for OHSS and some of them had previous history of severe OHSS and ICU admission after single maneuver for prophylaxis of OHSS. Also, serum AMH level wasn't the only limiting parameter for cases selection because previous history of severe OHSS and ICU admission may reflect patient susceptibility and also, AMH kits variability may reflect the lower levels in some cases of the study. As the cases are at high risk for OHSS, ethically GnRH antagonist protocol should be adopted and triggered with GnRH agonist and low dose of HCG is mandatory for better pregnancy outcome [15,16].

The pregnancy rate wasn't affected by this protocol. In this study, biochemical pregnancy rate was 48%, clinical pregnancy rate was 40%, and miscarriage rate was 4%. This is in comparison with Lin et al. in a retrospective study demonstrated statistically significant higher clinical pregnancy rate in dual triggering of final oocyte maturation with a combination of GnRH agonist and HCG than in the HCG trigger group (50.7 vs 40.1%) [27]. In contrast Engmann et al. reported comparable clinical pregnancy success rates in a fresh embryo transfer cycle in which oocyte maturity has been triggered by GnRH agonist after co treatment with GnRH antagonist, and the traditional HCG trigger after GnRH agonist preparation clinical pregnancy [56.7%] vs. [51.7%] [28] However Engmann et al. also, differs from what was seen in the cochrane review that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate (pregnancy beyond 12 weeks) and a higher rate of early miscarriage (less than 12 weeks) [29].

Table 1
Clinical characteristics of the treatment cycle.

	Min.–Max.	Mean. ± SD.
Maximum E2 level (pg/ml)	14.0–89.0	46.6 ± 20.1
Progesterone on HCG day (ng/ml)	0.10–1.0	0.4 ± 0.3
Endometrial thickness on HCG day (mm)	9.0–13.0	10.6 ± 1.2
Number of Gonadotrophin (75IU) ampoules	19.0–40.0	32.1 ± 6.7
Duration of stimulation (days)	9.0–12.0	11.3 ± 0.9

Table 2
Comparison between OHSS and non OHSS women characteristics.

	Non-OHSS (n = 38)	OHSS (n = 12)	*p*
Body mass index			
Min.–Max.	20.8–27.7	20.2–25.3	0.2
Mean. ± SD.	23.8 ± 2.2	22.6 ± 2.0	
Median.	23.4	22.8	
Basal FSH			
Min.–Max.	1.8–7.6	2.5–5.2	0.1
Mean. ± SD.	4.4 ± 1.7	3.4 ± 1.2	
Median.	4.3	2.9	
Basal LH			
Min.–Max.	1.6–11.6	2.3–5.8	0.2
Mean. ± SD.	4.9 ± 2.7	3.4 ± 1.3	
Median.	4.9	2.9	
Basal E2			
Min.–Max.	16.5–48.2	28.0–45.0	0.5
Mean. ± SD.	32.8 ± 6.7	34.8 ± 8.2	
Median.	32.0	31.5	
AMH			
Min.–Max.	2.5–7.4	4.0–5.0	0.7
Mean. ± SD.	4.5 ± 1.5	4.4 ± 0.4	
Median.	4.5	4.4	
Antral follicle number			
Min.–Max.	20.0–34.0	22.0–28.0	0.7
Mean. ± SD.	25.7± 3.7	25.0 ± 2.8	
Median.	24.0	25.0	
Number of gonadotropin(75IU) ampoules			
Min.–Max.	19.0–40.0	27.50–40.0	0.644
Mean. ± SD.	31.8 ± 7.2	33.3 ± 4.8	
Median.	33.0	33.0	
Number of Antagonist ampoules			
Min.–Max.	4.0–7.0	5.0–7.0	0.301
Mean. ± SD.	6.4 ± 0.8	6.0 ± 0.9	
Median.	7.0	6.0	
Days ofstimulation			
Min.–Max.	9.0–12.0	10.0–12.0	0.301
Mean. ± SD.	11.4 ± 0.8	11.0 ± 0.9	
Median.	12.0	11.0	

t: Student *t*-test.

As the treatment protocol in this study included a small dose of HCG, there was a potential risk of exacerbating OHSS. In our study, six cases (24%) developed early moderate OHSS, however, neither cases developed severe nor critical OHSS. In comparison with study by Griffin et al. reported only one case of mild OHSS in the dual-trigger group, and there were no cases of OHSS in the GnRH agonist trigger group however, neither severe nor critical cases were reported in both groups [30].

The small supplementary bolus of HCG clearly rescued the luteal phase after GnRH agonist triggering, resulting in a normal reproductive outcome. Thus, in the latest study (the largest randomized trial to date) including a total of 302 IVF/ICSI cycles – there was no significant difference in live birth rate between GnRH agonist triggering supplemented with a bolus of 1500 IU HCG after OPU and 10,000 IU HCG. Also, no cases of OHSS were seen in the GnRH agonist group versus 2% in the 10,000 IU HCG group [31].

The use of GnRH antagonist protocol resulted in a more physiological approach to ovarian stimulation, leading to fewer side-effects and complications than the long-agonist protocol. Additionally, when using GnRH antagonist protocol, GnRH agonists can be used to induce oocyte maturation. GnRH agonists can produce a short duration endogenous LH surge, (24–36 h), which is adequate to initiate oocyte maturation, but not to produce the prolonged stimulation of the corpus luteum as seen with the use of a traditional HCG trigger [32]. Expression of genes related to steroidogenesis is lower at the time of oocyte retrieval in patients triggered with GnRH agonist. The decreased expression of VEGF and inhibin B in the GnRH agonist triggered patients can explain the mechanism of early OHSS prevention [33].

In this study cabergoline didn't affect the pregnancy rate yet decreased the incidence of OHSS. This goes with what was found by Cochrane review that Cabergoline reduces the risk of OHSS in susceptible women, especially for moderate OHSS without affecting the pregnancy rate, clinical pregnancy rate, miscarriage rate or the risk of side effects [34]. Hosseini et al., also found that the incidence of OHSS was statistically significant ($P = 0.01$) lower in the cabergoline-treated group than in patients who did not receive cabergoline and at risk of OHSS (12% vs 36%) [35]. Carizza et al. compared early OHSS with late OHSS and found that cabergoline decreased the risk of early OHSS significantly (0.0 vs 15% $P < 0.001$), but the risk of late onset OHSS was not decreased (10.8 vs 3.8%), in comparison with no medication [36]. A study by Várnagy et al. demonstrated that OHSS incidence was statistically significant lower in cases received low-dose aspirin than in cases who did not receive it (0.25% vs.8.4%, $p < 0.001$) [37].

Majority of studies suggest an endometrial defect secondary to a lack of LH action, rather than a simple deficiency of estrogen and progesterone. As LH is important for up-regulation of growth factors such as VEGF A, fibroblast growth factor 2, cytokines involved in implantation and stimulation of extra gonadal LH receptors, all of these factors are important for normal implantation and early neovascularization. Additionally, low dose of HCG is less likely to cause OHSS because there is less VEGF production [31].

We concluded that, the use of low-dose aspirin, cabergoline, and low dose of HCG in combination with GnRH agonist for triggering ovulation in fixed GnRH protocol produces excellent clinical pregnancy rates, while almost totally avoiding admission to hospital with severe or critical OHSS.

Disclosure statement

There is nothing to disclose.

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