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Original Research Article

Evaluation of a therapeutic combination to prevent ovarian hyperstimulation syndrome

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ABSTRACT

Background: Ovarian hyperstimulation syndrome (OHSS) remains a significant iatrogenic complication in assisted reproductive technology. Various strategies have been proposed to minimize its occurrence, particularly in high-risk patients. To evaluate the effectiveness of a combined preventive protocol including GnRH antagonist protocol, GnRH agonist trigger, dopamine agonist (cabergoline), calcium infusion, and a freeze-all strategy in reducing the incidence of OHSS without compromising IVF outcomes.
Methods: A comparative study was conducted on women undergoing IVF, divided into a study group receiving the combined protocol and a control group managed conventionally. Primary outcomes included stimulation parameters, incidence of OHSS, and biochemical pregnancy rates. Secondary outcomes assessed included the number of cumulus-oocyte complexes (COCs), mature oocytes (MII), and vitrified embryos.
Results: The study group showed significantly lower gonadotropin doses, with improved ovarian response reflected by higher numbers of COCs, MII oocytes, and vitrified embryos ($p<0.05$). Despite these improved biological outcomes, β-hCG positivity rates did not differ significantly between the two groups (24% vs. 26.5%; $p=0.239$). No cases of moderate or severe OHSS were observed in the study group.
Conclusions: The combined use of multiple evidence-based strategies appears effective in reducing the risk of OHSS while maintaining satisfactory IVF outcomes. This multifaceted approach may offer a safer stimulation pathway for high-risk patients without compromising pregnancy potential.

Keywords: Ovarian hyperstimulation syndrome, In vitro fertilization, GnRH antagonist protocol, GnRH agonist trigger, Dopamine agonist, Cabergoline

INTRODUCTION

In the context of in vitro fertilization (IVF), controlled ovarian stimulation based on high doses of gonadotropins is not entirely without risk. It may lead to the development of ovarian hyperstimulation syndrome (OHSS), which is considered an iatrogenic complication. OHSS occurs in approximately 20–33% of cases in its mild form, 3–6% in its moderate form, and in 0.1–2% of cases in its severe form.[1-4] These rates may be even higher among high-risk women, such as those with polycystic ovary syndrome (PCOS).[5,6]

Clearly, prevention is preferable to treatment, particularly when dealing with an iatrogenic condition. Despite a better

understanding of stimulation protocols and disease pathophysiology, OHSS cannot be completely eliminated, and more effective measures are needed to reduce or even eliminate severe forms of the syndrome.[2]

The primary objective of our study was to assess a specific therapeutic combination used as a novel secondary prevention protocol for OHSS. Secondarily, we aimed to evaluate the impact of this combination on IVF outcomes.

METHODS

Study design, setting, and period

This was a prospective descriptive study conducted in the In Vitro Fertilization (IVF) Unit of Aziza Othmana Hospital, Tunis, Tunisia, from June 2017 to October 2019.

Selection criteria

The study included 91 women undergoing an antagonist IVF cycle who were identified as being at high risk for ovarian hyperstimulation syndrome (OHSS). Patients were considered at risk if they met one or more of the following criteria: number of follicles >10 mm ≥25 on the day of ovulation trigger, serum estradiol level >3500 pg/ml on the day of trigger, number of cumulus-oocyte complexes (COCs) retrieved ≥24.

Procedure

In accordance with the recommendations of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART), a preventive protocol for OHSS was applied as follows: 1) ovulation trigger: Two ampoules of Decapeptyl 0.1 mg were administered subcutaneously, with serum LH and progesterone levels measured 12 hours later, 2) cabergoline: 0.5 mg/day orally, starting on the day of ovulation trigger and continued for 8 days, 3) intravenous calcium infusion: 10 ml of 10% calcium gluconate in 200 mL saline was administered on the day of oocyte retrieval and repeated on days 2 and 3 post-retrieval, and 4) freeze-all strategy: All embryos were vitrified on day 2, 3, or 5, with delayed embryo transfer in subsequent cycles.

Outcome measures

Early signs of OHSS were assessed on days 2, 3, and 7 after oocyte retrieval. Symptomatic patients underwent pelvic ultrasonography to evaluate ovarian size and ascitic fluid. In cases where OHSS was suspected, laboratory investigations were performed, including complete blood count, serum electrolytes, total proteins, and renal and liver function tests (see Appendix 1).

IVF outcomes in the high-risk group (Group E) were compared with those of a control population (Group P) who underwent fresh embryo transfer during the same period.

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Aziza Othmana Hospital, Tunis, and all participants provided written informed consent prior to inclusion.

Statistical analysis

Data were analyzed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean±standard deviation (SD) or median (interquartile range). Comparisons between groups were made using Pearson's chi-square test for categorical variables and Student's t-test for continuous variables with normal distribution.

A p value <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the 91 women in the study group (Group E) are presented in Table 1.

Table 1: Baseline characteristics of the study population (Group E, n=91).

Variable	Mean±SD/ N (%)	Range/notes
Age (years)	33.06±4.38	22–43
Nulligravidae	—	Majority (exact n not given)
Duration of infertility (years)	5.74±3.77	2–21
Unexplained infertility	57 (63)	—
PCOS profile	41 (45)	—
Severe OATS in spermogram	6/36 (16.6)	Based on 36 spermograms
AMH (ng/ml)	3.47±1.28	—
Antral follicle count (AFC)	13.18±4.51	—

The average age was 33.06 years, with most women being nulligravidae.

Polycystic ovary syndrome was observed in 45% of cases, and unexplained infertility accounted for 63%.

The average starting dose of gonadotropins was 229.23±47.24 IU, with a total dose of 2102.68±707.54 IU. The mean estradiol level on the day of trigger was 5558.76±3379.42 pg/ml.

The mean number of developed follicles was 23.9±12.94 (range 9 to 67). The mean number of follicles >15 mm at trigger was 16.38±8.55 (range 1 to 40).

Out of 91 women, 5 were lost to follow-up. Among the 86 followed-up patients, 76 underwent frozen embryo transfers, with 5 patients receiving three transfers in total.

Regarding the number of vitrified embryos, a statistically significant difference was observed between the "negative β-hCG" and "positive β-hCG" subgroups in favor of the latter (p=0.03). No significant difference was found for other parameters, particularly the number of MII oocytes and oocyte maturity (p=0.147 and p=0.256, respectively).

Table 2: Biological outcomes of the IVF cycle in the study group.

Variable	Mean	Standard deviation
CCO name	19.21	10.528
MII name	12.04	7.371
MI name	0.73	1.096
VG name	1.35	1.980
Number of Degenerated oocytes	4.89	4.756
Number of zygotes	7.75	5.246
Oocyte maturity	0.60	0.54

OHSS occurrence

No cases of severe early OHSS were observed.

One patient was hospitalized for moderate OHSS (pelvic pain, hematocrit 40%, mildly enlarged ovaries without ascites). Hospital stay was short (4 days) with rapid clinical, biological, and ultrasound improvement.

Thirteen women (14.28%) were mildly symptomatic at day 3 post-retrieval: 10 (10.98%) reported mild abdominal pain, and 3 (3.29%) had nausea without vomiting; among them, 5 had PCOS. Table 3 shows the incidence and severity of OHSS in the study group.

Table 3: The incidence and severity of OHSS in the study group.

OHSS Severity	Number of Patients	Percentage (%)
No OHSS	77	84.62
Mild OHSS	13	14.28
Moderate OHSS	1	1.10
Severe OHSS	0	0

Comparative analysis with general population (Group P)

The two groups were comparable in demographics: mean age 33.06 (E) vs. 32.7 (P), p=0.905; mean BMI 20.03 (E) vs. 21.96 (P), p=0.213.

Infertility duration was longer in the study group (5.74 years vs. 4.88 years).

Table 4: Demographic and baseline characteristics comparison.

Parameter	Group E (n=91)	Group P (n=91)	P value
Mean age (years)	33.06	32.7	0.905
Mean BMI (kg/m²)	20.03	21.96	0.213
Infertility duration (years)	5.74	4.88	—

Significant differences were found for day 3 estradiol (p=0.002) and ovarian reserve markers (AFC p=0.036; AMH p=0.015), which were higher in group E.

Most stimulation parameters and IVF outcomes differed significantly between groups (p<0.05). Despite lower gonadotropin doses in group E (starting dose 229.23 IU and total 2102.68 IU vs. 284.65 IU and 3100 IU in group P), a higher number of COCs, MII oocytes, and vitrified embryos were obtained.

No significant difference was found in β-hCG rates: positive β-hCG was 24% in group E and 26.5% in group P (p=0.239). In other words, the therapeutic combination had no impact on IVF success rates. Table 5 summarise this results.

Table 5: Comparative analysis of IVF results with the general population.

Variable	Group P (n=1268)	Group E (n=91)	P value
Starting dose of gonadotropins (IU/ml)	284.65 ±301.4	229.23 ±187.3	<0.001
Total dose of gonadotropins (IU/ml)	3100 ±2961.1	2102.68 ±1765.4	<0.001
E2 on the day of triggering (pg/ml)	1420 ±1501.4	5558.76 ± 5479.1	<0.001
Number of follicles ≥15 mm	8.58 ±7.54	16.38 ±17.06	<0.001
CCO name	14.89 ±13.11	23.93 ±24.57	0.001
Number of vitrified embryos	1.57 ±1.04	4.32 ±4.57	<0.001

DISCUSSION

Ovarian hyperstimulation syndrome (OHSS) remains one of the major iatrogenic complications of IVF cycles. Its pathophysiology is primarily based on increased capillary permeability, leading to a fluid shift into the third space. The central role of hCG, whether endogenous or exogenous, in triggering OHSS is well established. It induces the expression of vascular endothelial growth factor (VEGF) and its receptor VEGFR2—key mediators of angiogenic response and vascular hyperpermeability.[7]

In our study, the combination of several preventive strategies resulted in improved stimulation parameters without increasing the risk of OHSS or adversely affecting pregnancy outcomes. While β-hCG positivity rates did not differ significantly between the two groups, the biological and embryological outcomes were clearly superior in the study group.

Effect of the combined approach on OHSS prevention

Cabergoline

Cabergoline, a dopamine agonist, has been shown to reduce VEGFR2 phosphorylation and thus vascular permeability. Several studies, including a 2021 Cochrane review, have confirmed its efficacy in reducing the incidence of moderate to severe OHSS (OR 0.32), with no adverse effects on clinical pregnancy or live birth rates. In our study, cabergoline use was associated with improved stimulation parameters and appeared to contribute to OHSS risk reduction1.

GnRH antagonist protocol

The use of a GnRH antagonist protocol is widely recognized for its protective effect against OHSS. A 2020 meta-analysis by Kaddoura and several RCTs have demonstrated significantly reduced OHSS incidence with this protocol (RR 0.58), as well as lower gonadotropin requirements and shorter stimulation durations. In our cohort, the study group required significantly lower gonadotropin doses, supporting the effectiveness of the antagonist strategy.[8-10]

GnRH agonist for final oocyte maturation: Triggering ovulation with a GnRH agonist instead of hCG significantly reduces the risk of OHSS. Recent data show not only a protective effect but also improved oocyte yield and embryological outcomes. In our protocol, this approach likely contributed to reduced OHSS risk while maintaining comparable pregnancy rates.[11,12]

Freeze-all strategy

Vitrification of all embryos in high responders is now a validated strategy for OHSS prevention. It allows dissociation of the stimulation phase from the high-risk luteal phase. In our study, the number of vitrified embryos was significantly higher in the study group, with no increase in complications, further supporting the freeze-all approach.

A Cochrane meta-analysis, published and updated in 2021, reported similar findings. Indeed, the incidence of OHSS was lower with a "Freeze-All" strategy (OR 0.26, 95% CI 0.17 to 0.39; $I^2 = 0\%$; 6 randomized controlled trials, 4,478 women; low certainty evidence). No significant differences were found in terms of cumulative clinical pregnancy rates (OR 0.95, 95% CI 0.75 to 1.19; $I^2 = 31\%$; 4 studies, 1,245 women) or cumulative live birth rates (OR 1.08, 95% CI 0.95 to 1.22; $I^2 = 0\%$; 8 randomized trials, 4,712 women).[13]

Calcium infusion

Intravenous calcium gluconate has been reported to inhibit renin-angiotensin system activation and reduce VEGF production. While evidence remains limited, promising results show reduced OHSS incidence (RR 0.14). Its inclusion in our protocol may have contributed to the overall protective effect.[14]

Impact on IVF outcomes

The main benefit of our combined preventive strategy was observed in ovarian stimulation outcomes: a higher number of COCs, MII oocytes, and vitrified embryos, despite significantly lower gonadotropin doses. These findings suggest improved stimulation efficiency with a favorable safety profile.

In contrast, β-hCG positivity rates were not significantly different between groups. This aligns with several meta-analyses suggesting that OHSS prevention strategies, such as cabergoline or antagonist protocols, do not negatively impact clinical pregnancy or live birth rates.[15]

Limitations

This study has some limitations, including the absence of long-term follow-up on live birth rates and potential heterogeneity in ovarian response. Further large-scale prospective randomized trials are warranted to confirm our findings and optimize preventive therapeutic combinations.

CONCLUSION

Our findings suggest that a multimodal preventive strategy combining a GnRH antagonist protocol, GnRH agonist trigger, cabergoline, calcium infusion, and a freeze-all approach can significantly improve ovarian stimulation outcomes while reducing the risk of OHSS, without compromising pregnancy outcomes. This synergistic approach aligns with current literature supporting individualized, physiology-based prevention of OHSS. Continued research is necessary to validate these results and establish standardized guidelines for combined prophylactic interventions in high-risk patients.

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