Ovarian hyperstimulation syndrome: steps to maximize success and minimize effect for assisted reproductive outcome

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Objective: To investigate the strategies used to decrease the risk of ovarian hyperstimulation syndrome (OHSS) and their impact on pregnancy and live birth rates.
Design: Retrospective cohort analysis.
Setting: University hospital.
Patient(s): One hundred eighty-eight patients undergoing fresh in vitro fertilization (IVF) cycles between 2000 and 2004, with peak serum estradiol levels >2500 pg/mL and presumed to be at risk for OHSS.
Intervention(s): Coasting and elective embryo cryopreservation were evaluated for their effect on OHSS and live birth rates.
Main Outcome Measure(s): Pregnancy, live birth rates, and OHSS incidence.
Result(s): Out of 188 patients at risk for OHSS, 21 patients had their cycles coasted (group 1), and elective embryo cryopreservation was performed in 32 patients (group 2). In 135 patients with no other risk factors, ovulation was triggered with human chorionic gonadotropin and embryo transfer was performed (group 3). The incidence in our IVF population was 38 out of 1002 (3.8%). The overall incidence of OHSS for those who had an estradiol level >2500 pg/mL was 20.2% (38 out of 188), and none of the patients in group 1 developed OHSS; 13 out of 32 patients in group 2 (40.6%) and 25 out of 135 (18.5%) patients in group 3 developed OHSS. The live birth rate was 38%, 40%, and 45% in groups 1, 2, and 3, respectively, and the cumulative live birth rate was 52%, 75%, and 59%, respectively.
Conclusion(s): Elective cryopreservation of embryos with subsequent frozen embryo transfer and coasting are effective ways of maximizing pregnancy and limiting severe OHSS. (Fertil Steril® 2010;94:173–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: Coasting, elective embryo cryopreservation, OHSS, ovarian hyperstimulation syndrome

Although considerable improvement has been seen in the pregnancy outcomes with the introduction of new stimulation protocols, the incidence of ovarian hyperstimulation syndrome (OHSS) has failed to decrease over time. Ovarian hyperstimulation syndrome is a potentially life-threatening complication associated with controlled ovarian hyperstimulation and in vitro fertilization (IVF). Increased vascular permeability and fluid shifts cause hemoconcentration, which may be complicated by renal failure, thromboembolic episodes, respiratory distress, and death. The enlarged ovaries after controlled ovarian hyperstimulation can potentially rupture, hemorrhage, or undergo torsion (1, 2).

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Despite extensive research, the pathogenesis of this syndrome is unclear. The variables closely related to OHSS are beta human chorionic gonadotropin (β-hCG), serum estradiol (E_2), the number of follicles, vascular endothelial growth factor (VEGF), interleukin-6, the ovarian renin angiotensin system, and prostaglandins (1, 3–5).

Though high serum E_2 levels are most often associated with an increased risk of OHSS (6), the syndrome has been reported to occur with extremely low E_2 levels as well (7, 8). Various strategies have been proposed to reduce the occurrence of this syndrome, but none can eliminate the risk completely while maintaining optimum pregnancy outcome.

Cycle cancellation lowers the risk of OHSS but at the expense of losing the cycle (9). Withholding the hCG injection until the serum E_2 falls below an acceptable level, commonly called *coasting,* decreases the incidence of OHSS and, although the implantation rate in a coasted cycle is reported to be lower, the pregnancy rates still reach 38.5% (10). Likewise, elective cryopreservation of the embryos with subsequent transfer at a later time has also been shown to reduce OHSS, and the cumulative live birth rate per patient with this technique approaches 82% (11).

We performed a retrospective data analysis at the Division of Reproductive Endocrinology and Infertility of the Mayo Clinic in Rochester, Minnesota, to ascertain whether we could minimize the incidence and severity of ovarian hyperstimulation while maximizing the chances of a successful pregnancy outcome in patients thought to be at risk for OHSS.

MATERIALS AND METHODS

The medical records of all consecutive patients who underwent fresh IVF cycles between 2000 and 2004 with long luteal gonadotropin-releasing hormone (GnRH) down-regulation protocol were screened. All patients with peak serum E_2 levels of >2500 pg/mL were presumed to be at increased risk for OHSS based on prior clinical observation, and they constituted our study population. Out of a total of 1002 IVF patients, 188 patients were considered to be at increased risk for OHSS.

Informed consent was obtained by use of prior authorization for research, and approval was granted by the institutional review board. The data collected from these patients were then analyzed to determine [1] what percentage of patients thought to be at increased risk for OHSS based on their E_2 value of >2500 pg/mL were actually diagnosed with the syndrome, and [2] what the strategies were used to decrease the risk of OHSS and their impact on pregnancy and live birth rates (LBR). Patients with OHSS were also divided into three categories on the basis of symptoms, signs, and limitation of activity. Mild manifestations of OHSS included nausea, vomiting, and diarrhea abdominal discomfort and distension; moderate OHSS included worsening of symptoms, ascites, and ovarian enlargement up to 12 cm; and severe OHSS constituted pain accompanied by rapid weight gain, tense ascites, hemodynamic instability, respiratory difficulty, progressive oliguria, and laboratory abnormalities. Placement of patients in group 1, 2, or 3 was decided with respect to increased symptoms (as described for moderate/severe OHSS). If the symptoms and signs were milder, the patients were in group 1; whereas if the symptoms were more severe, patients were included in group 2. Patients were placed in group 3 when there was an increased level of E_2, increased follicles, and few OHSS symptoms.

Statistical analysis was performed using the JMP 9.0 software (SAS Institute, Cary, NC). Analysis of variance was used, and $P<.05$ was considered statistically significant.

RESULTS

The overall incidence of OHSS in our study population was 20.2% (38 out of 188). Out of 188 patients, 21 (11.1%) had their cycles coasted (group 1), and elective embryo cryopreservation was done in 32 (17%) patients (group 2). In the remaining 135 (71.8%) patients, who had no risk factors other than a high E_2, ovulation was triggered with hCG, and embryo transfer (ET) was performed (group 3). The decision to coast, cryopreserve, or trigger ovulation was based upon the developing follicles, serum E_2 level, and clinical judgment. The age, infertility diagnosis, and basal level of follicle-stimulating hormone (FSH) of the patients in all the three groups were similar. Peak E_2 levels on the day of hCG injection were also comparable ($P>.05$, not statistically significant). Although none of the patients in group 1 developed OHSS, 13 out of 32 (40.6%) in group 2 and 25 out of 135 (18.5%) patients in group 3 developed OHSS (Tables 1 and 2).

In group 1 (n = 21), coasting was done if E_2 levels were >2500 pg/mL with a large cohort of small developing follicles (>30). The aim was to allow the follicles to develop without stimulating more E_2 production and still permit retrieval. The peak E_2 level was 3489.0 ± 410 pg/mL, and the mean number of days of coasting was 1.1 ± 0.4. It is our policy to cancel a cycle if a >30% drop in E_2 levels occurs during coasting, but none of the patients in this group had their cycles canceled for this reason. The serum E_2 value on the day of hCG administration was 3031.8 ± 663 pg/mL. The average number of oocytes retrieved in group 1 was 15.7 ± 4.7, and 2.42 ± 0.5 embryos were transferred. The biochemical pregnancy rate (BPR) was 52.4%, LBR per ET was 38%, and none of the patients developed OHSS, as determined by clinical symptoms (see Table 1).

The embryo cryopreservation group (group 2, n = 32) had a peak E_2 level of 3541 ± 1040 pg/mL, and the average number of oocytes retrieved equaled 25.5 ± 6.6. The embryos were then frozen at pronuclear stage for use at a later date (see Table 1). Three out of 32 patients did not undergo frozen embryo transfer (FET); two conceived spontaneously, and one was an overseas patient who was lost to follow-up observation. A total of 55 FETs were performed in 29 patients. On average, each patient underwent 1.89 ± 1.23 FET cycles. The postthaw pronuclear embryo survival rate was 94.2%, and 2.34 ± 0.6 embryos were transferred. The overall LBR per transfer was 40%. The cumulative LBR to date per patient has approached 75%. In this group, 48.2% of the patients (14 out of 29) had a live birth on the first attempt at FET. The mean number of days from retrieval to first FET was 90 ± 38, and by day 581, all patients had used all their frozen embryos (Table 3). Although 13 out of 32 patients developed OHSS in this group, none developed severe OHSS (see Table 2).

In the final group (group 3, control, n = 135), who underwent routine stimulation and fresh ET, the peak E_2 level was 3084.7 ± 465.9 pg/mL. The average number of oocytes retrieved was 17.0 ± 5.5, and 2.5 ± 0.7 embryos were transferred. The BPR was 65.9%, and the LBR per ET was 45%. It is interesting that 25 out of 135 (18.5%) patients developed OHSS. Severe OHSS occurred in two patients: one patient developed middle cerebral artery occlusion, and one patient had ovarian torsion (see Tables 1 and 2).

DISCUSSION

The published incidence of OHSS is 20% to 33 % for mild, 3% to 6 % for moderate, and 0.1% to 2.0% for severe OHSS, and our results agreed with this range (12–14). The