CASE REPORT

Critical ovarian hyperstimulation syndrome in a ‘coasted’ in-vitro fertilization patient

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We report an instance of critical ovarian hyperstimulation syndrome in a highly responsive in-vitro fertilization patient despite the preventive measure of a 4 day ‘coast’ interval during which no gonadotrophins were administered while gonadotrophin-releasing hormone agonist therapy continued until serum oestradiol concentrations fell below 3000 pg/ml.

Key words: ’coast’/in-vitro fertilization/ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of superovulation therapy. The characteristic features of severe OHSS are sequelae of profuse vascular exudation, resulting in the accumulation of fluid in potential spaces at the expense of a greatly diminished effective arterial volume. Critical OHSS is a recently described sub-classification of severe OHSS in which the symptoms manifested are imminently life threatening (Navot et al., 1992). These symptoms include profound haemoconcentration, adult respiratory distress syndrome, thromboembolic disease, and renal failure.

In an effort to avoid the significant financial and emotional toll that in-vitro fertilization (IVF) cycle cancellation incurs, alternative strategies for the prevention of OHSS have been developed. They include the i.v. administration of albumin (Shalev et al., 1995) or hydroxyethyl starch solution at the time of oocyte retrieval (Graf et al., 1997), early or repeated follicle aspiration (Amir et al., 1993), laparoscopic ovarian electrocautery prior to gonadotrophin therapy (Rimington et al., 1997), total embryo cryopreservation with delayed uterine transfer (Titiinen et al., 1995), and ‘coasting’.

Coasting entails the withdrawal of exogenous gonadotrophin and the withholding of human chorionic gonadotrophin (HCG) administration until the patient’s serum oestradiol decreases to a ‘safer’ level, arbitrarily established as < 3000 pg/ml. The existing literature has demonstrated a very small incidence of severe OHSS among highly responsive patients who have coasted. Urman et al. (1992) used this technique in 40 hyperstimulated gonadotrophin cycles and achieved clinical pregnancy and severe OHSS rates of 25% and 2.5% respectively. Ben-Nun et al. (1993) examined 66 coasted IVF–embryo transfer cycles and showed a 24% clinical pregnancy rate with no instances of severe OHSS. Sher et al. (1995) reported a 41% clinical pregnancy rate and no cases of severe OHSS among 51 coasted IVF–embryo transfer patients. Benadiva et al. (1997) studied 22 coasted IVF–embryo transfer patients and reported no severe OHSS among them. Their clinical pregnancy and OHSS rates were equivalent to similar patients who underwent embryo cryopreservation and delayed transfer.

In a recent retrospective study, we noted three instances of severe OHSS occurring among 44 highly responsive coasted IVF–embryo transfer patients (6.8%). Of note, all cases occurred in patients who had achieved oestradiol concentrations \( \geq 4000 \text{ pg/ml} \) at the time of meeting the follicular criteria for HCG administration (Tortoriello et al., 1998). We now report a case of critical OHSS occurring in a coasted IVF patient to further emphasize the imperfect nature of ‘coasting’ as a method for the prevention of OHSS in very highly responsive IVF patients.

Case report

The patient is a 40 year old Hispanic female, who presented to our centre with complaints of secondary infertility of 4 years’ duration. She reported regular heavy menses since menarche at age 12. In 1982, the patient underwent a left salpingectomy for an ectopic pregnancy. Her past medical history and review of systems were significant only for iron-deficiency anaemia.

A complete infertility work-up revealed tubal obstruction and severe teratozoospermia in her husband (2% normal forms by Kruger’s strict criteria). The decision was made to proceed with gonadotrophin superovulation, intracytoplasmic sperm injection and embryo transfer.

On day 3 of her menstrual cycle, the patient’s follicle stimulating hormone (FSH) and oestradiol concentrations were 4.2 mIU/ml and 47 pg/ml respectively. (In our centre, FSH values \( > 10 \text{ mIU/ml} \) are associated with poor outcome and this serves as our cut-off for IVF candidacy.) The patient underwent a modified flare protocol. On day 5 of her cycle, the patient initiated a 21 day course of pituitary–ovarian suppression with oral contraceptive pills (Ortho-Novum 1–35®; Ortho, Raritan, NJ, USA). Upon completion of this 3...
week period, her oestradiol level was 30 pg/ml and a transvaginal ultrasound revealed ovarian quiescence. Two days thereafter, the patient started gonadotrophin-releasing hormone agonist (GnRHa) therapy with leuprolide acetate (Lupron®; Tap, Chicago, IL, USA) 0.5 mg s.c. twice daily. After 2 days of GnRHa, the patient added highly purified urinary FSH (Fertinex®; Serono, Randolph, MA, USA), 150 IU s.c. twice daily, to her regimen. After 6 days of this combined therapy, her oestradiol concentration was 2078 pg/ml, and transvaginal sonography revealed multiple small follicles, all < 16 mm in diameter. She continued this regimen and returned in 2 days. Despite an oestradiol level of 5238 pg/ml, her follicular cohort still did not meet our criteria for the administration of HCG, requiring at least five follicles > 16 mm in average diameter, two of which must be at least > 19 mm in average diameter. The patient’s dose of FSH was halved and she returned the next day. By this time, her follicular cohort met our criteria and contained 12 follicles that were at least 16 mm in average diameter. As her oestradiol level at this time was 5686 pg/ml, she was directed to discontinue gonadotrophin therapy and to continue GnRHa therapy as a measure for the prevention of OHSS. Daily transvaginal ultrasonography for follicle measurements was also discontinued at this point. She took no FSH that evening, but mistakenly administered an additional 150 IU of FSH the next morning. Thereafter however, she maintained only GnRHa therapy until her serum oestradiol concentrations fell below 3000 pg/ml. On the second day of her coast interval, the patient achieved a peak pre-ovulatory oestradiol level of 12 859 pg/ml (Figure 1). When her oestradiol level had fallen to 2775 pg/ml after 4 days of coasting, the patient administered 10 000 IU HCG. Approximately 34 h later, 10 oocytes were retrieved via transvaginal follicular aspiration under i.v. sedation. Two days after her oocyte retrieval, the patient had three embryos transferred, one at the 2-cell stage, and two at the 3-cell stage. Assisted zona hatching with Tyrode’s solution was performed prior to transfer. The patient orally administered vibramycin 100 mg and medrol 8 mg twice daily starting the evening prior to oocyte retrieval and continuing until 2 days after embryo transfer. For luteal support, the patient received 25 mg progesterone in oil intramuscularly on the day of her retrieval and thereafter administered 50 mg daily.

Two days after her embryo transfer, the patient returned to our centre complaining of mild shortness of breath, abdominal fullness, and occasional light-headedness. She reported no noticeable reduction in her urine output. Her pulse was 104 and her blood pressure was 100/70 without orthostatic changes. Her abdomen was mildly distended. The patient’s weight was 63 kg. Her pre-treatment height and weight were 160 cm and 61 kg, respectively. The remainder of her physical examination was normal. Her white blood cell count was 27 200 and her haematocrit was 43.3%. Her pre-retrieval values were 8800 and 30.1%, respectively. Against medical advice, the patient refused hospital admission in favour of oral hydration, bed rest, and close outpatient surveillance. The patient was contacted by phone that evening and reported one episode of emesis. Reassessment of the patient the following morning revealed a deterioration of her clinical status. Her abdomen was more tense, her breathing was more laboured, and her resting pulse rate was 116. A transvaginal ultrasound revealed enlarged ovaries (left: 10.2 cm×5.3 cm; right: 9.2 cm×5.1 cm) with significant ascites. At this point, the patient agreed to hospitalization. Upon admission, her white blood cell count was 29900 and her haematocrit was 44.9%. On the basis of her haematocrit shift, by this time the patient had lost ~ 47% of her total plasma volume (van Beaumont, 1972). The patient’s serum albumin level had fallen to 2.6 gm/dl (normal 3.5–5.6 gm/dl).
Her blood urea nitrogen and creatinine concentrations were 21 and 1.0 mg/dl. Her electrolytes and prothrombin and partial thromboplastin times were within normal limits. She was i.v. hydrated with 5% dextrose in 0.9 normal saline at 125 ml/h and observed carefully. On hospital day 2, the patient’s weight had increased to 65 kg. Her abdominal girth measured 86.5 cm. Pulmonary auscultation revealed decreased breath sounds at the lung bases. A chest X ray with abdominal shielding revealed small bilateral pleural effusions. With hydration, the patient’s white blood cell count and hematocrit had improved to 17,700 and 32%, respectively. Her blood analyses, however, revealed elevated liver transaminases with an aspartate aminotransferase (AST) level of 46 IU/l (normal <30 IU/l) and an alanine aminotransferase (ALT) of 81 IU/l (normal <45 IU/l). At this point, the patient was still experiencing dyspnoea and was utilizing supplemental oxygen by nasal cannula. As she was maintaining adequate oral intake with urine output >100 ml/h, the rate of her i.v. hydration was decreased. By hospital day 3, the patient’s weight and abdominal girth had decreased to 64 kg and 86 cm respectively. Her white blood cell count and hematocrit further improved (13,200 and 28.4% respectively). Her liver function tests remained elevated however; her AST and ALT were 49 and 87 IU/l respectively. The gamma glutamyl transferase concentration was also noted to be elevated at 127 IU/l (normal <55 IU/l). As her oral intake and urine output continued to be adequate, the patient’s i.v. fluid rate was further decreased. By hospital day 4, the patient’s hematocrit had decreased to 24%. Her dyspnoea and pulmonary examination were significantly better, although a repeat chest X ray demonstrated persistence of the right-sided pleural effusion. The patient’s i.v. hydration was discontinued and overnight she diuresed copiously. On the morning of hospital day 5, the patient was feeling much better. Her lung examination continued to improve. Her weight had reduced to 63 kg and her abdominal girth had decreased to 82.5 cm. Her labs revealed resolution of her haemoconcentration and improvement of her transaminities. She was discharged that afternoon to follow-up as an outpatient. She was to take iron supplementation and to continue her progesterone regimen.

When the patient presented to our centre 2 days later she had no complaints. Her abdominal distension was much improved. Her lungs were clear to auscultation. Her weight had decreased to 61 kg. When she returned 3 days later, exactly 2 weeks after her embryo transfer, a serum b-HCG was noted to be negative.

Discussion

By virtue of her very severe degree of haemoconcentration, the patient described in this case report manifested critical OHSS. She also exhibited hepatic injury, pleural effusions, significant ascites, and respiratory compromise.

Approximately 5 days after she administered 10,000 IU HCG, the patient began to experience the symptomatology of OHSS. This onset is characteristic of the ‘early’ form of OHSS, believed to be induced by the exogenous HCG utilized to precipitate pre-ovulatory oocyte maturation (Dahl Lyons et al., 1994).

In this patient, as with most coasted patients, oestradiol concentrations continued to rise briefly before ultimately decreasing during the coast interval. As is customary, HCG was administered when her serum oestradiol concentration fell below 3000 pg/ml. Despite her 4 day coast interval, critical OHSS developed. One can only speculate about the severity of the patient’s OHSS had she not coasted or had she become pregnant, but it quite possibly could have been worse. It is also possible that the patient may have increased her risk for OHSS by mistakenly administering an additional 2 ampules of FSH. Nonetheless, this report further weakens the notion that excessive gonadotrophin stimulation can be offset by a lengthy period of gonadotrophin withdrawal.

This patient’s clinical course establishes that a threshold of ovarian stimulation can exist beyond which a coast interval will not reliably prevent even the most severe degree of OHSS. The basic premise of ‘coasting’, that the decline of follicular oestradiol production associated with gonadotrophin withdrawal indirectly signifies diminished overall responsiveness of the granulosa cell cohort, is therefore rendered questionable. This report, as well as previous reports recounting severe OHSS occurrences among superovulation patients enzymatically incapable of oestradiol production (Levy et al., 1996; Meirow et al., 1996), serves to remind the practitioner of the unreliable role of pre-ovulatory oestradiol concentrations in the prediction of OHSS. The criterion established for the termination of a coast interval (oestradiol < 3000 pg/ml) therefore offers false reassurance regarding a patient’s potential to develop severe OHSS subsequent to HCG administration.

In conclusion, we report a case of critical OHSS occurring in a highly responsive IVF–embryo transfer patient despite a prolonged period of gonadotrophin withdrawal. This bolsters the suggestion that coasting be used only with the greatest caution in the most highly responsive IVF–embryo transfer patients (i.e. oestradiol > 4000 pg/ml on the day of meeting follicular criteria) until data is accrued which conclusively demonstrate its preventive effect upon the occurrence of OHSS. At this time, cycle cancellation remains the only definitive method to prevent OHSS in such patients.

References


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