Dual renin–angiotensin blockade therapy in patients at high risk of early ovarian hyperstimulation syndrome receiving IVF and elective embryo cryopreservation: a case series

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BACKGROUND: Ovarian hyperstimulation syndrome (OHSS) is an important and dangerous aspect of assisted reproduction techniques. Although elective cryopreservation of all embryos can prevent pregnancy-induced late OHSS, it cannot prevent early OHSS, which is induced by hCG administration. METHODS: We undertook this trial to assess the efficacy with which the combined oral administration of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) could prevent early OHSS in IVF patients at very high risk for this syndrome. Four women, who had serum estradiol concentration >8000 pg/ml on the day of hCG injection, were treated with the combination of the ACEI alacepril and the ARB candesartan cilexetil for 8 days starting the day after oocyte retrieval. Embryos were cryopreserved and embryo transfer was postponed until later cycles. RESULTS: Despite the extremely enlarged ovaries, no ascites was accumulated in any of the cases. Haematocrit (34.1 ± 1.0) and serum albumin concentration (4.1 ± 0.2 g/dl) were normal throughout the treatment period. These patients showed elevated plasma renin and angiotensin II concentration before the treatment. CONCLUSIONS: The dual renin–angiotensin blockade therapy used here would be worth exploring further in a study with more patients and a prospective, randomized design.

Key words: angiogenesis/angiotensin-converting enzyme inhibitor/AT1 receptor antagonist/early OHSS/embryo cryopreservation

Introduction

Severe ovarian hyperstimulation syndrome (OHSS) is a potentially lethal iatrogenic complication of ovulation induction. Although an approach consisting of elective cryopreservation of all embryos and their subsequent transfer in non-stimulated cycles has been proposed for those at risk of OHSS (Amso et al., 1990), it can prevent only pregnancy-associated late OHSS. Early OHSS is associated with the administration of hCG. At present, there is insufficient evidence to support routine cryopreservation for prevention of early OHSS (D’Angelo and Amso, 2002). The most effective approach to prevent OHSS is cycle cancellation and the withholding of hCG. Although it is the safest approach, the choice of cycle cancellation is frustrating and costly to the infertile patient. Several other approaches have been undertaken to prevent OHSS, including coating (Sher et al., 1995), early timed oocyte retrieval (Tomazevic and Meden-Vrtovec, 1996), glucocorticoid administration (Tan et al., 1992), intravenous administration of albumin (Shoham et al., 1994), use of recombinant LH instead of urinary hCG (The European Recombinant LH Study Group, 2001) and the prolonged use of GnRH agonist (Rizk and Smitz, 1992). None of these approaches has consistently demonstrated superiority in the prevention of severe early OHSS in those patients at extremely high risk for this syndrome.

Early OHSS may be associated with intense angiogenesis in the multiple corpora lutea, in which the capillary network is immature and thus leaky during its development. We hypothesized that early OHSS may be triggered by hCG-induced ovarian renin–angiotensin system (RAS) activation. For the prevention of life-threatening severe or critical OHSS, elective cryopreservation of all embryos and ovarian RAS blockade would be an ideal combination. Although overstimulation of RAS has been proposed as one of the possible modes of pathogenesis of OHSS (Navot et al., 1987; Ong et al., 1991; Morris and Paulson, 1999), there has been only one human study in which luteal phase steroid production was decreased by captopril in oocyte donors at particularly low risk.
of OHSS (Morris et al., 1995a). Here we report the first successful combined use of an angiotensin-converting enzyme inhibitor (ACEI) and an AT1 antagonist, which is clinically called an angiotensin II receptor blocker (ARB), in combination with routine cryopreservation for the prevention of early OHSS in four women at very high risk for this syndrome.

**Patients and methods**

This approach was approved by the Institutional Review Board of Nagoya University Hospital in October 2001. All of the four patients, who were included in this study between October 2001 and August 2002, presented a high level of serum estradiol (E2) on the day of hCG administration (E2 >8000 pg/ml) and a high number (30 or more) of follicles of intermediate or large size (diameter ≥12.0 mm). Informed written consent was obtained from each patient after the purpose and nature of the study had been fully explained. The mean patient age was 32.8 ± 2.2 years. The mean body mass index was 20.8 ± 0.9 kg/m².

The ovarian stimulation protocol was similar for all patients. We used a down-regulation protocol with 900 µg/day of GnRH agonist (nafarelin acetate; Yamanouchi, Tokyo, Japan) and urinary FSH (Nikkken, Tokyo, Japan). The average amount of the administered FSH was 1706.3 ± 308.5 IU. All patients were administered 10 000 IU of hCG (Teikokuzoki, Tokyo, Japan) 35 h before oocyte retrieval. The average serum E₂ at hCG injection was 9036.3 ± 1220.9 pg/ml. The peak haematocrit was 34.1 ± 1.0, and the peak number of white blood cells/mm³ was 8125 ± 2204.

Blood sampling for renin, angiotensin I (Ang I) and angiotensin II (Ang II) was performed after each patient in the study group lay in a supine position for 30 min. The blood samples were collected in tubes containing EDTA (disodium salt) and immediately centrifuged at 4°C. The resultant supernatant plasma samples were immediately frozen at −20°C and assayed at Mitsubishi Kagaku Bio-Clinical Laboratories, Inc. (Tokyo, Japan). Renin concentration (1.05 pg/ml) was measured by immunoradiometric assay. Ang I (100 pg/ml) and Ang II (4 pg/ml) concentrations were measured by radioimmunoassay. Plasma vascular endothelial growth factor (VEGF, 15.6 pg/ml) was measured by enzyme immunoassay. Intra/inter-assay CV was <6% for each assay.

**Results**

No patient suffered from moderate or severe OHSS. There was only limited or no ascites retention after oocyte retrieval despite the enlarged ovaries (mean diameter: 59.3 ± 4.4 mm) on day 7 post-retrieval. Neither haemoconcentration nor low albuminaemia was observed throughout the luteal phase (Table I). None of the patients required hospitalization. No hypotension or other major side effect of the drugs was observed. It should be noted that all of four recent similar cases that were not treated here suffered from severe or moderate OHSS (data not shown).

The plasma renin and Ang II concentrations were high before administration of ACEI and ARB (Table I). The plasma Ang II concentration was reduced by 61.0% but was still high 5 or 6 days after the treatment in spite of the ACEI administration (Table I). However, the plasma VEGF concentration was normal in all patients (≤38.4 pg/ml).

**Discussion**

OHSS was completely prevented by using combined ACEI and ARB in four patients who were at very high risk for this syndrome.

Luteinization after ovulation of the enlarged ovary requires extensive angiogenesis during the early luteal phase. VEGF is the best known vasoactive substance released by the post-ovulation ovaries, but Ang II may also be such a substance. In rabbit ovaries in vitro, exposure to hCG enhances both the rate of ovarian secretion of Ang II and the intrafollicular content of Ang II (Yoshimura et al., 1994). Ang II is known to initiate angiogenesis (Fernandez et al., 1985) and increase vascular permeability (Robertson and Khairallah, 1972). VEGF has been demonstrated to be the major capillary permeability factor in OHSS ascites (McClure et al., 1994). It has been shown that angiogenesis induced by VEGF is so intense that it is very leaky (Thurston et al., 1999). Recent studies have demonstrated that Ang II upregulates VEGF locally (Otani et al., 1998; Richard et al., 2000; Tamarat et al. 2002). More interestingly, the Ang II angiogenic effect may also involve macrophage activation and cyclooxygenase-2 enhancement (Tamarat et al. 2002). In addition to symptomatic improvements, all of our patients showed serological findings that indicated reduced severity of OHSS. Extremely high concentrations of plasma renin and Ang II would have indicated that there was cryptic severe OHSS in our cases. However, the elevation of the Ang II level was not completely suppressed following the administration of ACEI. We assume that ACEI might be only partially effective in the combination therapy. The dose of ACEI that could be used was limited in our small series due to dry cough, which is a typical minor side effect of ACEI due to the accumulation of bradykinin, another substrate for ACE. Plasma VEGF, whose level is
correlated with the clinical picture of OHSS (Abramov et al., 1997), was low in each case. It is likely that administration of the two antihypertensive drugs from the day after oocyte retrieval prevented strong angiogenesis during the early luteogenesis.

Combination therapy with ACEI and ARB has been established in not only hypertensive but also normotensive diseases such as IgA nephropathy (Russo et al., 1999). We chose the combination therapy because it acts at two distinct levels: AngII synthesis and AT1 receptors. One possible explanation of the effectiveness of our approach is that the combination therapy may more completely prevent the luteal angiogenesis caused by the portion of Ang II produced despite ACEI treatment and/or by the residual amount of Ang II produced via a non-ACE-dependent pathway, such as human chymase (Urata et al., 1993). There have been some animal studies using ACEI or ARB. Administration of enalapril in OHSS-induced rabbits has been reported to cause a 40% decrease in the incidence of the syndrome, although the definition of OHSS in rabbits is different from that in women (Morris et al., 1995b). On the other hand, a few other reports failed to show the prevention of OHSS by ACEI (Sahin et al., 1997; Gul et al., 2001). A single drug might be insufficient to block ovarian RAS. Furthermore, in all of those reports, ACEI was administered from the same day that hMG injection was started, and therefore the effects of the drug on steroidogenesis, ovulation, follicular growth and oocyte maturation should have been involved in the results obtained. The ovarian RAS theory is still controversial. It could be argued that the increase in the RAS activity in OHSS patients may be secondary to the third space fluid shifts and may be renal and not ovarian in origin. However, in all of our patients, RAS was activated, but neither haemoconcentration nor low albuminaemia occurred. In accordance with our current clinical data, we recently have obtained pathological data on reduced angiogenesis using an ACEI- and ARB-treated rabbit OHSS model (unpublished data). In conclusion, here we studied a limited number of patients at the highest risk for severe OHSS and were able to prevent OHSS completely. Further clinical and basic research studies will be required to evaluate the dual RAS blockade therapy for the prevention of early OHSS.

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