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BACKGROUND: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation, and the pathophysiological mechanisms that trigger the syndrome remain unknown. HCG increases serum vascular endothelial growth factor (VEGF) concentrations, and VEGF modulates transendothelial permeability via endothelial adherens junctions, a downstream target for VEGF signalling. We examined whether women with severe OHSS have altered serum levels of soluble vascular endothelial (sVE)-cadherin. METHODS: We conducted a prospective, case-control study of 28 women with severe OHSS and 34 women undergoing controlled ovarian hyperstimulation (COH) for IVF without developing OHSS. We collected serum samples from both groups on the day of ovum retrieval (Day 0), and on Days 3, 6, 9 and 15. Samples were assayed for sVE-cadherin by enzyme-linked immunosorbent assay. RESULTS: Women with severe OHSS had significantly higher levels of sVE-cadherin than patients without OHSS (P < 0.001). sVE-cadherin serum levels decreased with clinical improvement; however, they did not reach normal levels in the resolution phase. A positive correlation was demonstrated between sVE-cadherin and serum estradiol levels at the time of HCG administration (r = 0.621; P < 0.001). Serum sVE-cadherin levels were more closely chronologically correlated with corpus luteum function than with biological and clinical aspects of severe OHSS. CONCLUSIONS: sVE-cadherin may be involved in the pathogenesis of severe OHSS and may possibly serve as an indicator of corpus luteum function after COH.

Keywords: capillary permeability; endothelium; vascular endothelial-cadherin; vascular endothelial growth factor; ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening condition associated with ovarian stimulation such as that employed in preparation for IVF and ICSI. The pathophysiological mechanism of OHSS is unknown and treatment continues to be empirical. Severe cases include the development of critical conditions associated with ascites, ovarian enlargement, pleural and pericardial effusion, hypovolemia with hemoconcentration and hypotension with oliguria (Schenker and Weinstein, 1978; Balasch et al., 1998). OHSS occurs in 0.1–4% of ovulation induction treatments (Navot et al., 1992), and the incidence is increasing worldwide due to the increase in infertility treatments.

Many vasoactive and angiogenic cytokines, such as vascular endothelial growth factor (VEGF) (McClure et al., 1994; Abramov et al., 1997), have been implicated in the pathogenesis of OHSS. The role of cell adhesion molecules that mediate inflammatory and immune reactions has been previously investigated (Chen et al., 1999; Daniel et al., 1999; Abramov et al., 2001).

We (Pellicer et al., 1999; Gómez et al., 2002, 2003) and others (Abramov et al., 1996) have shown that certain inflammatory cytokines (interleukin-6, tumour necrosis factor-α, and interleukin-1) and VEGF may be crucial in the pathophysiology of the systemic acute phase response in OHSS; however, not all authors agree (Geva et al., 1999; Enskog et al., 2001; Mathur et al., 2002; Babayof et al., 2006). A rapidly expanding body of data has revealed the importance of endothelial cells in the evolution and propagation of inflammatory process in many human tissues; these cells support leukocyte adhesion and extravasation through the vessel wall, which are key steps in human response to infection and tissue injury (Albert et al., 2002).

Endothelial cells have tight and adherens junctions that have a general organization similar to that described for epithelial cells (Aberle et al., 1996; Gumbiner, 1996). Endothelial cells express a cell-specific cadherin called vascular endothelial
VE-cadherin, also known as CD144/cadherin-5 (Ranscht, 1994; Dejana et al., 1999; Angst et al., 2001). Angst et al. (2001) as well as other groups (Hudy-Clergeon et al., 2005) clearly showed that VE-cadherin is exclusively expressed in endothelial cells. Although the extracellular domain of VE-cadherin is required for homophilic adhesion and clustering, its intracellular association to catenins and the cytoskeleton is needed for stabilization of the junctional complex and for full control of paracellular permeability (Navarro et al., 1995). In addition, catenins released into cytoplasm may translocate to the nucleus and modulate cell transcription (Takeichi, 1993; Bienz and Cleves, 2000). This suggests that the cadherin–catenin complex may play a role in intracellular signal transduction following homotypic cell-to-cell adhesion.

VE-cadherin plays a key role in regulating endothelial cell permeability and migration, as well as the assembly of new blood vessels (Takeichi, 1993; Navarro et al., 1995; Vittet et al., 1996; Bienz and Cleves, 2000). Endothelial adherens junctions are a known downstream target for VEGF signalling; tyrosine phosphorylation is involved in the loosening of cell–cell contacts and thereby modulates transendothelial permeability (Esser et al., 1998).

Previously, we investigated the potential involvement of VE-cadherin in capillary hyperpermeability in an in vitro OHSS model (Villasante et al., 2007). We observed that both HCG and VEGF, but not high doses of estradiol (E2), produced significant changes in VE-cadherin concentration in human umbilical vein endothelial cells (HUVEC) cultures; treating cultures with anti-human VEGF antibodies prevented these changes. Additionally, permeability assays demonstrated that HCG and VEGF caused changes in the actin fibres, indicating increased capillary permeability. VEGF also induced an increase in the paracellular permeability of HUVEC cultures. Therefore, we demonstrated that VE-cadherin played a role in the development and progression of increased capillary permeability in an in vitro model of OHSS. However, in vivo data were still lacking.

The purpose of this study was to investigate whether the endothelium was a source and target of the vasoactive substances released in response to the conditions clinically induced in women who develop OHSS. We focused specifically on the release of VE-cadherin, a component of the adherens junction strand and the endothelial barrier. We evaluated serum levels of soluble forms of VE-cadherin (sVE-cadherin) in women following controlled ovarian hyperstimulation (COH) for IVF/ICSI.

Materials and Methods
The institutional human subjects review board at our centre approved all procedures, and the informed written consent was obtained from all participants. Each participant received a complete evaluation protocol prior to COH, including clinical history, physical and ultrasound examination and hormonal profile.

Patients
The study group comprised 28 women with severe OHSS, all of whom were healthy infertile women, 32.1 ± 0.7 years old (mean ± SEM), who had undergone ovulation stimulation for IVF treatment (Table I). OHSS was diagnosed and graded according to the classification proposed by Bellver et al., (2003). Criteria included massive ovarian enlargement (>5 cm (mean ovarian size, 6.7 ± 3.5 cm), massive ascites with or without hydrothorax, laboratory evidence of hemococoncentration as demonstrated by increased haematocrit (>45% (mean, 47.7 ± 1.2%) or leukocyte count >15,000 mm−3 (mean, 17,050 ± 550 mm−3) and the collection of >20 oocytes during oocyte retrieval. In its severe form, OHSS includes clinical evidence of breathing difficulties, ascites and oliguria. Markedly elevated serum E2 levels (mean, 3747 ± 315.3 pg/ml) were also observed in all study patients. Ten pregnancies (35.7%) related to the ovulation induction treatment course occurred in the study group.

Stimulation protocol
All 28 patients were treated according to similar ovarian stimulation protocols for IVF that included recombinant FSH (rFSH) (Gonal-F; Serono, Madrid, Spain) plus HMG (Menopur; Ferring, Madrid, Spain) and 250 µg of recombinant HCG (Ovitrelle; Serono). In addition, a GnRH agonist (Triptorelin; Decapeptyl 0.1; Ipsen Pharma, Barcelona, Spain) or GnRH antagonist (Ganirelix; Orgalu-tran, Organon, Barcelona, Spain) was administered to the patients (19 patients received the agonist and 9 patients the antagonist), according to two different protocols. Briefly, pituitary desensitization was initiated with daily s.c. administration of 0.1 mg Triptorelin, which was administered from the mid-luteal phase of the previous cycle until the day of menses. The GnRH antagonist was started when one follicle reached a mean diameter of 14 mm. When pituitary suppression was documented (serum E2 level <30 pg/ml [100 pmol/l] and serum progesterone <0.3 ng/ml [1 mmol/l]) and ovarian quiescence was demonstrated via vaginal ultrasound following menstruation, the standard protocol started with 150 IU rFSH and 75 IU HMG, daily. Serum E2 and progesterone, serial pelvic examinations and

| Table I. Demographic, clinical and laboratory data of the study and control groups. |
|---------------------------------|---------------------------------|--------------------|
| Study group                  | Control group                  | P                  |
| (n = 28)                      | (n = 34)                       |                    |
| Age (years)                   | 32.1 ± 0.7                     | 33 ± 0.9           | NS                 |
| BMI (kg/m²)                   | 24.1 ± 1.5                     | 26.1 ± 1.5         | NS                 |
| Basal FSH                     | 6.9 ± 0.5                      | 7.1 ± 0.5          | NS                 |
| Basal LH                      | 7.5 ± 0.9                      | 5.3 ± 0.5          | 0.049              |
| Infertility length (years)    | 2.5 ± 0.2                      | 2.8 ± 0.3          | NS                 |
| Cause of infertility          |                                 |                    |                    |
| Male factor                   | 14 (50)                        | 12 (35.2)          | NS                 |
| Polycystic ovaries            | 8 (28.6)                       | 4 (11.8)           | NS                 |
| Tubal factor                  | 0 (0)                          | 2 (5.9)            | NS                 |
| Endometriosis                 | 2 (7.1)                        | 1 (2.9)            | NS                 |
| Unexplained                   | 4 (14.2)                       | 15 (44.1)          | 0.013              |
| Treatment length (days)       | 11.2 ± 0.44                    | 11.1 ± 0.3         | NS                 |
| Gonadotrophin dose (IU)       | 2234 ± 229.4                   | 3299 ± 274.9       | 0.006              |
| E2 level [pg/ml]              | 3747 ± 315.3                   | 1825 ± 156.7       | 0.001              |
| Ovarian size [mm]             | 67.2 ± 3.5                     | 49.9 ± 3.6         | 0.001              |
| # ova retrieved               | 21.3 ± 1.6                     | 16 ± 1.6           | 0.028              |
| # metaphase II                | 16.1 ± 1.3                     | 12.6 ± 1.6         | NS                 |
| # embryos                     | 11.6 ± 1.2                     | 2.5 ± 0.8          | NS                 |
| Cryopreserved embryos         | 3.2 ± 0.9                      | 9 ± 1.4            | NS                 |
| Pregnancies (PR/ET %)         | 10 (35.7)                      | 16 (47)            | NS                 |
| Implantation rate (%)         | 20 (24.8)                      |                   | NS                 |
| Twins (%)                     | 4 (44.4)                       | 4 (25)             |                    |

Note: Values are presented as mean ± SEM or n (%). NS, not significant; BMI, body mass index; PR, pregnancy rate; ET, embryo transfer; E2, estradiol.

Both groups underwent controlled ovarian stimulation for IVF but only the study group developed ovarian hyperstimulation syndrome (OHSS). *On day of HCG administration.
vaginal sonography were used to monitor patients as required. This protocol was modified when the patient presented risk factors of hyperstimulation or poor response in her clinical history, ultrasound examination, or hormonal assessment. Polycystic ovary syndrome (PCOS), defined as oligomenorrhea and hyperandrogenism, was especially considered for COH. From Day 3 of stimulation onwards, gonadotrophin administration was individualized according to serum levels and ovarian response, as documented by ultrasound.

When at least two leading follicles reached a mean follicular diameter of 18 mm, 250 µg of HCG was administered. GnRH agonist and antagonist and gonadotrophin injections were discontinued on the day of HCG administration. Transvaginal oocyte retrieval was scheduled for 36 h after HCG injection using an ultrasound-guided approach.

Control group

We enrolled a matched control group consisting of 34 women undergoing COH for IVF, who did not develop OHSS. Controls were healthy women (33 ± 0.9 years old) who were matched to the study group by age, fertility treatment and pregnancy rate (Table I). Twenty-seven patients received GnRH agonists and seven received GnRH antagonist. Sixteen pregnancies (47%) related to the ovulation induction treatment course occurred in the control group.

In both groups, two to three embryos were transferred on the Day 3 of development. Luteal phase support included 400 mg/day intravaginal micronized progesterone (Progeffik 200; Efik, Madrid, Spain) that was started the day after oocyte retrieval and maintained until a pregnancy test was performed, or until Day 80 of pregnancy if the patient tested positive. No patients received HCG for luteal support. Serum β-HCG levels were monitored on the 15th day after oocyte retrieval.

Study protocol

Five blood samples were obtained by venipuncture from each patient in both groups. Sample 1 was obtained at the time of the oocyte retrieval (basal control), sample 2 was obtained at the day of embryo transfer, samples 3 and 4 were obtained and 9 days after oocyte retrieval and the last sample was obtained at the day of the pregnancy test (15 days after oocyte retrieval).

All 28 patients with severe OHSS were managed and monitored on an outpatient basis, but they required more careful evaluation than the control group, including frequent physical and ultrasound examinations (to detect increasing ascites), daily weight measurements, abdominal girth measurements, fluid intake, urine output and routine blood parameter measurements (complete blood count and coagulation parameters, electrolytes, liver and renal function). Careful monitoring was essential and included at least daily communication, to ensure that progression to more severe disease was promptly recognized. The patients were treated with antiemetics, potent analgesics, furosemide if needed, i.v. colloid and crystalloid solutions (Pellicer and Garcia-Velasco, 2002). Routinely administered colloid solutions included hidroxyletilenstarch (PM 200.000/0.6) 6% (ELOHES®, Fresenius Kabi, Barcelona, Spain) and human albumin, 20% (Grifols Institute, Barcelona, Spain). The routinely administered crystalloid solution was 0.9% normal saline. Solutions were administered daily and titrated according to oral fluid intake, urine output and haemodynamic variables. Abdominal paracentesis for tense ascites was performed as needed. Patients were advised to avoid strenuous physical activity because it is associated with a risk of ovarian torsion when ovaries are significantly enlarged, and patients were advised to avoid intercourse because it might be painful and could increase the risk of ovarian rupture (Pellicer and Garcia-Velasco, 2002). Pregnant patients with OHSS were monitored very closely because the risk of progressing to severe disease is particularly high for those further stimulated by the pregnancy-associated rapid rise in serum HCG concentration.

Hormone assay

Serum E2 was measured using microparticle enzyme immunoassay technology and employing the Axysym System (Abbot Laboratories, IL, USA). The intra- and inter-assay coefficients of variation (CVs) were <13.9%. Haemoglobin, haematocrit and leukocytes were measured using the Cell-Dyne 3200 (Abbot Laboratories), with intra- and inter-assay CVs < 2.1, 6.0 and 5.7%, respectively.

Determination of VE-cadherin concentrations

All the blood samples were centrifuged at 900 x g for 10 min at room temperature, and the cell-free supernatants were stored immediately in aliquots at –80°C until assayed collectively by an investigator (AV) who was blinded to patient assignment.

Soluble VE-cadherin levels were measured in duplicate using a commercially available enzyme-linked immunosorbent assay kit (Bender MedSystems, Vienna, Austria). Intra- and inter-assay CVs were 4.1 and 7.2%, respectively. No cross-reactivity between soluble VE-cadherin and other adhesion molecules has been found using this assay.

Statistical analysis

Categorical data were expressed as number and percentage, and numerical data as mean (±SEM). Statistical analyses performed were Chi-Square test, Fisher test, analysis of variance and analysis of covariance. Correlations between laboratory variables and levels of soluble VE-cadherin were tested by using the Pearson product moment correlation test. Univariate logistic regression analysis was used to demonstrate the association between serum levels of VE-cadherin and the development of OHSS. A P-value <0.05 was considered statistically significant for all comparisons. Statistical analysis was performed using the Statistical Package for Social Sciences version 10.0 (SPPS Inc., Chicago, IL, USA).

Results

Relevant clinical data for the study and control groups are given in Table I. On admission, high haematocrit and leukocyte counts were recorded for all patients with OHSS, indicating haemoconcentration. Mean haematocrit was 47.7 ± 1.2%, mean haemoglobin level was 14.3 ± 1.8 g/dl, and mean leukocyte count 17 050 ± 550 cells/mm³. All patients with OHSS showed marked ascites, while five (17.9%) had hydrothorax. The mean creatinine level was 0.86 ± 0.03 mg/dl. Gastrointestinal symptoms (diarrhoea and/or vomiting) were present in 10 patients with OHSS (35.7%).

Figure 1 shows the changes of VE-cadherin levels during clinical course of severe OHSS. Compared with controls, patients with OHSS had significantly higher serum levels of soluble VE-cadherin at the different time points studied. Soluble VE-cadherin levels decreased along with clinical improvement (i.e. Day 15 after HCG, if no pregnancy occurs, should be the time when patients are symptom free); however, they did not reach normal values in the resolution phase (i.e. after HCG is tested, either menstrual period with negative HCG, or pregnant).

The following factors independently increased the risk for developing OHSS: young age, low body weight, PCOS,
higher doses of exogenous gonadotrophins, high absolute or rapidly rising serum E2 levels, previous episodes of OHSS, number of developing ovarian follicles, and the number of oocytes retrieved in assisted reproductive technology cycles. Statistical correlations between sVE-cadherin levels and risk factors were calculated for the OHSS group by using the Pearson product moment correlation test. A significant correlation was found between concentration of soluble VE-cadherin on Day 6 and E2 serum levels, at the time of HCG administration (r = 0.621; P < 0.001; Table II and Fig. 2). Furthermore, there was a trend towards a positive correlation with the number of oocytes retrieved (r = 0.312; P = 0.08). Nevertheless, no significant correlation was observed between the serum levels of VE-cadherin and other laboratory or clinical parameters of OHSS.

Univariate logistic regression analysis did not show an association between serum levels of VE-cadherin, the day of oocyte retrieval and the development of OHSS, (odds ratio = 4.33; P = 0.118).

**Discussion**

To our knowledge, this is the first report of increased serum sVE-cadherin levels in women with severe OHSS. Our previous in vitro study results using HUVEC cultures suggest that this soluble cell adhesion molecule may play a role in the pathophysiology and progression of OHSS (Villasante et al., 2007).

We wanted to assess whether VE-cadherin is involved in this intraovarian and systemic response in which exaggerated leukocyte recruitment and transendothelial migration appears to cause tissue damage and capillary hyperpermeability. Here, we report the follow-up on 28 patients who developed severe OHSS and later clinically improved. During the acute phase of the syndrome, high levels of sVE-cadherin were detected in the serum of all patients and were accompanied by clinical features of capillary leakage and haemoconcentration. sVE-cadherin concentration decreased after a clinical improvement but did not return to basal levels when extracellular fluid accumulation and haemoconcentration had resolved.

Our results agree with several published observations that suggest the involvement of cell adhesion molecules in ovarian physiology (Campbell et al., 1995; Mantzavinos et al., 1996; Vigano et al., 1997, 1998). These data suggest that cell adhesion molecules and the immune system may play a role in physiologic ovarian processes such as folliculogenesis, ovulation, corpus luteum formation and luteolysis, and as suggested by our findings, in the pathophysiology of OHSS that results from the exaggeration of these processes.

The participation of cell adhesion molecules, which are major mediators of inflammation, in ovarian physiology and pathophysiology is not surprising; there are many indications that inflammation may play an important physiological role in ovarian reproductive processes (Daniel et al., 1999). Rupture of the follicle during ovulation may depend on tissue remodeling, which is similar to an acute inflammatory reaction and includes mobilization of thecal fibroblasts, increased leukocyte migration, release of various mediators and loosening of connective tissue elements in the follicle wall (Mori et al., 1996).

On the other hand, the expression and shedding of VE-cadherin is up-regulated by inflammatory cytokines that are ubiquitous in patients with OHSS (Gómez et al., 2002; Albert et al., 2002). In accordance with this hypothesis, we previously reported that VEGF stimulated the secretion of VE-cadherin from endothelial cells in a dose-dependent manner. Furthermore, we demonstrated that HCG stimulation elevates VE-cadherin concentrations in HUVEC cultures, possibly explaining the progression of OHSS during pregnancy.

**Table II.** Correlation between serum E2 levels on the day of HCG administration (day +15) and soluble vascular endothelial-cadherin levels at different time points.

<table>
<thead>
<tr>
<th>Times</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocyte retrieval/ n = 26</td>
<td>0.314</td>
<td>0.155</td>
</tr>
<tr>
<td>Embryo transfer/ n = 22</td>
<td>0.350</td>
<td>0.155</td>
</tr>
<tr>
<td>Day +6/ n = 33</td>
<td>0.621</td>
<td>0.001</td>
</tr>
<tr>
<td>Day +9/ n = 32</td>
<td>0.315</td>
<td>0.102</td>
</tr>
<tr>
<td>β-HCG determination/ n = 12</td>
<td>0.643</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Day + x days after oocyte retrieval.
However, E₂ did not affect the release of VE-cadherin (Villasante et al., 2007). High absolute or a rapidly rising serum E₂ level is a risk factor for developing OHSS, and although excess E₂ increases capillary permeability of the uterus and ovarian vessels, it is not an absolute, unique mediator of HCG. High doses of estrogens do not by themselves induce clinical hyperstimulation. On the basis of clinical observations, we know that if E₂ levels are abnormally high but HCG has not been administered there is generally no OHSS (Pellicer and Garcia-Velasco, 2002), as HCG and not E₂ may release the vascular mediators that start the syndrome.

Trophoblast formation and invasion is accompanied by the expression of sVE-cadherin (Wang et al., 2002, 2004). Therefore, pregnancy, which is a risk factor for OHSS progression, causes a non-significant increase in sVE-cadherin, accounting for part of the disease progression observed in cycles that result in conception. In support of this hypothesis, (Mantzavinos et al., 1996) reported that concentrations of other adhesion molecules, such as intracellular adhesion molecule (ICAM-1)-1, were significantly higher in cycles that resulted in conception than in cycles that did not.

The reasons for the self-limiting nature of OHSS during pregnancy remain unclear. If HCG administration had a key role in triggering or promoting OHSS, we would expect the clinical symptoms to worsen progressively during early pregnancy because HCG concentrations increase consistently during early gestation. However, there is no correlation between OHSS progression and increasing HCG concentrations during early pregnancy (Ludwig et al., 1998). Perhaps the recovery of local capillary permeability and the leakage of fluid from the ovaries are responsible for the self-limiting of OHSS. Therefore, the serial monitoring of VEGF and VE-cadherin concentrations may have prognostic value.

We have shown here that women who did not develop OHSS after COH had significantly lower serum sVE-cadherin levels than their counterparts with OHSS. Thus, we propose that soluble VE-cadherin is released by ovarian endothelium and mesothelial blood vessels and may play a role in the transudation of fluid and proteins into the peritoneal cavity in OHSS patients. In conjunction with another group of adhesion molecules, for example, E-selectin, ICAM-1 and vascular cell adhesion molecule-1, soluble VE-cadherin may participate in the 'rolling' movement, adhesion, extravasations, recruitment and activation of leukocytes and endothelial cells at sites of inflammation (Gearing et al., 1993).

Serum levels of VE-cadherin were more closely chronologically correlated with corpus luteum function than with biological and clinical aspects of severe OHSS. We found that serum levels VE-cadherin were positively correlated with serum levels of E₂ at the time of HCG administration and non-significantly—although a trend was observed—with the number of ova retrieved, both of which are known risk factors for the development of OHSS (Navot et al., 1992; Ludwig et al., 1998). So far, no specific prognostic marker that accurately predicts the course of OHSS has been identified, and serum concentrations of VE-cadherin after HCG administration may serve as clinically useful in this regard. There is enough evidence in the literature to identify HCG as the main trigger of OHSS, and we demonstrated that the addition of increasing doses of HCG to HUVEC cultures produced a significant increase in VE-cadherin concentration (Villasante et al., 2007). Therefore, levels of VE-cadherin may serve as an indicator of corpus luteum function after COH, which indirectly reflects the risk of OHSS development.

This study has several limitations. The study group only included symptomatic patients and excluded patients with minor stages of the syndrome. Therefore, it is difficult to make any firm conclusions about OHSS as a whole and several points should be emphasized: (i) this is the first report documenting increased levels of sVE-cadherin in patients with OHSS, and further studies are required to corroborate our results. In addition, it is unknown whether levels of sVE-cadherin fluctuate during the menstrual cycle. (ii) In vivo experiments, we measured sVE-cadherin levels from blood samples obtained during IVF treatment; however, a significant proportion of the molecules are bound to tissue receptors, making free-molecule concentrations an unreliable representation of the total number of molecules present. (iii) Biological alterations in OHSS or certain treatment methods may have interfered with evaluation of adhesion molecules in our study. For example, elevated leukocyte counts may increase serum cytokine concentrations and induce production of endothelial-cell-leukocyte adhesion molecules (Mori et al., 1996). We do not know whether the elevation in serum levels of sVE-cadherin is the result or the cause of the increase leukocyte count or coagulation disturbances. And (iv) the physiologic significance of elevated concentrations of sVE-cadherin is unknown. These soluble isoforms retain their binding capacity in vivo and thus can function in two ways: by triggering a biologic response and by competing in cell–cell junctions, thereby inhibiting cell adhesion.

Given these caveats, our results support a role for sVE-cadherin in the pathogenesis and progression of OHSS, and sVE-cadherin may serve as an indicator of corpus luteum function after COH.

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