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Hypercoagulability, high tissue factor and low tissue factor pathway inhibitor levels in severe ovarian hyperstimulation syndrome: possible association with clinical outcome

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During ovarian gonadotrophin stimulation for ovulation induction or *in vitro* fertilization, a clinical severe ovarian hyperstimulation syndrome (OHSS) may occur. Only few studies have investigated the mechanism responsible for the alterations of the haemostatic system in women affected by severe OHSS. The aim of the present study was to investigate the correlation between the magnitude of ovarian stimulation and the increase in fibrin formation and degradation in severe OHSS. Twenty-five patients (age range 23–43 years) who were hospitalized for severe OHSS, 25 women undergoing *in vitro* fertilization who did not develop OHSS (case–control group) and 25 healthy age-matched women (healthy control group) were investigated. On the day of admission a number of haemostatic markers, including D-dimer, thrombin–antithrombin complexes (TAT), prothrombin fragment 1 + 2 (F1 + 2), plasmin–antiplasmin complexes (PAP), tissue factor (TF), tissue factor pathway inhibitor (TFPI) and von Willebrand factor antigen (vWF), were examined. In patients with severe OHSS, TF, D-dimer, TAT, F1 + 2, PAP and vWF antigen plasma levels were significantly higher than those observed both in the case–control group and in healthy controls, whereas TFPI levels were significantly lower ($P < 0.005$) with respect to both case–controls and healthy controls. D-Dimer levels were related with serum oestradiol levels and oocyte number recovered ($r = 0.45$, $P < 0.001$ and $r = 0.47$, $P < 0.001$, respectively). D-Dimer and TAT levels were significantly ($P < 0.05$ and $P < 0.005$, respectively) higher in OHSS patients with unsuccessful pregnancy outcome (D-dimer, 226.5, 56–1449 ng/ml; TAT, 19.8, 3.1–82.6 μg/l) with respect to those with successful outcome of pregnancy (D-dimer, 145, 29–330 ng/ml; TAT, 5.0, 1.0–19.6 μg/l). Our data indicate that a marked hypercoagulability with alterations of TF and TFPI levels is detectable in patients with severe OHSS and that it is related to the clinical outcome. *Blood Coagul Fibrinolysis* 14:277–282 © 2003 Lippincott Williams & Wilkins.

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Introduction

The ovarian hyperstimulation syndrome (OHSS) is a well-known and serious complication that may occur in women who undergo controlled ovarian hyperstimulation (COH) cycles with gonadotrophins. This iatrogenic condition is characterized by a wide spectrum of clinical and laboratory manifestations including multicystic ovarian enlargement, rapid weight gain, massive extravascular fluid accumulation, combined with intravascular volume depletion, haemoconcentration, leukocytosis, oliguria and electrolytic imbalance [1]. Rare, but life-threatening, complications following the severe forms of OHSS have been reported, such as thromboembolism, hypovolaemic shock, liver dysfunction, renal failure and adult respiratory distress syndrome [2–4].

A precise model to explain the pathophysiology of the syndrome has not yet been elucidated. Several mediators involved in ovulation have been proposed as factors leading to OHSS such as oestrogens, histamine, cytokines, prostaglandins [5,6] and the ovarian renin–angiotensin system [7–10]. The major factor responsible for OHSS development seems to be human chorionic gonadotrophin (hCG) [11], exogenously administered or endogenously produced or, less frequently, luteinizing hormone [12].

Changes in the haemostatic system have been reported to be responsible for an increased thrombotic risk in these patients [13–19], but few studies investigated the mechanisms responsible for the alterations of the haemostatic system in women affected by severe OHSS. In particular, the role of plasma tissue factor (TF) and of tissue factor pathway inhibitor (TFPI) has

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not been studied until now. TF in complex with activated factor VII (FVIIa) plays a crucial role in the initiation of blood coagulation under normal and pathological conditions [20], and TF expression is induced in monocytes, endothelial cells and vascular smooth muscle cells following activation by proinflammatory cytokines or growth factors [21]. The TF:FVIIa activity is tightly regulated by TFPI. TFPI is a Kunitz-type serine protease inhibitor with a potent activity on the FVIIa/TF complex in the presence of activated factor X and with a direct inhibiting activity on activated factor X [22–25].

The present study was undertaken to investigate hypercoagulability, its correlation with the magnitude of ovarian stimulation and its possible predictive value for clinical outcome and involvement of TF and TFPI in severe OHSS.

Materials and methods

Patients

Twenty-five consecutive patients (age 22–43 years) admitted to the Obstetrics and Gynecology Department of University of Florence, Italy, for severe OHSS defined according to the criteria of Golan [26] were prospectively included in our study starting from May 1998 until December 2000. The patients had undergone *in vitro* fertilization and embryo transfer (IVF-ET) treatment for tubal factors and/or male factor indicators. All patients with severe OHSS presented ovarian enlargement, ascites, difficulty of breathing and oliguria. Twenty-five consecutive women in whom OHSS did not occur (case–control group) after induction of ovulation were matched by age (23–42 years) and duration of treatment. In addition, 25 apparently healthy age-matched (age 22–43 years) women (healthy control group) were selected as controls. No pregnant woman or woman on the contraceptive pill was included. Patients, case–controls and healthy controls had no personal or familial thromboembolic antecedents and did not present any known risk factor for thromboembolism. They were enrolled into this study after having given their informed consent to the use of part of their blood samples for an experimental study.

In vitro fertilization-embryo transfer

All patients underwent controlled ovarian hyperstimulation IVF-ET. Patients received the gonadotrophin-releasing hormone analogue triptorelin (Decapeptyl, Ipsen, France), 0.1 mg subcutaneously daily, from the mid-luteal phase until hCG administration. Multiple follicular development was induced by urinary-FSH (Metrodin HP; Serono Pharma, Rome, Italy) or recombinant-FSH (α-follitropin; Gonal F 75, Serono) at a subcutaneous dosage of 150 UI/day. COH was monitored by serum oestradiol (E_2) determination and transvaginal scanning (Aloka SSD 630, Tokyo, Japan) starting from day 6 of gonadotrophin administration. When at least three follicles > 17 mm in diameter were observed and oestradiol levels had reached ≥ 800 pg/ml, a subcutaneous dose of 10 000 UI hCG (Profasi HP, Serono, Italy) was administered. After 34–36 h, oocytes were recovered by transvaginal oocyte pick-up. Three to four embryos (three in women < 35 years, four in women > 35 years) were transferred at day 2 or day 3 from oocyte collection.

The luteal phase was supported by the daily intramuscular injection of 50 mg natural progesterone (Prontogest, Amsa, Italy). A pregnancy was recorded when a rise in serum (β-subunit) of hCG > 50 UI on day 14 after oocyte retrieval occurred and evidence of a gestational sac with embryo heart beat was visualized to the ultrasound scan after a further 2 weeks.

Successful pregnancies occurred in 11 of 25 patients after the IVF cycle.

In case OHSS signs or symptoms developed, the patient was invited to have another ultrasound scan and, in the presence of severe OHSS, she was hospitalized.

Haemostatic studies

Blood samples for haemostasis investigation were obtained immediately after hospitalization (on average 12 days, range 5–30 days, after hCG administration according to hospital admission for precocious or 'late form' severe OHSS) and before any heparin treatment. In the case–control group, blood samples were obtained during the mid-luteal phase of treatment cycle. Venous blood was collected from the antecubital vein without venous stasis, using a 19-gauge needle, in tubes (Vacutainer, Becton Dickinson, Meylan, France) containing 0.129 mol/l concentration of sodium citrate (final ratio with blood 1/10).

Blood samples were preserved and centrifuged at 4°C [for prothrombin fragment 1 + 2 (F1 + 2), thrombin–antithrombin complex (TAT), plasmin–antiplasmin complex, (PAP), TF and TFPI assay] or at 18°C [for D-dimer, von Willebrand factor (vWF) assay] (2000 × *g* for 10 min), and plasma was rapidly frozen in liquid nitrogen and stored at −80°C. Within 7 days, aliquots of plasma were thawed and used for analytical determinations.

F1 + 2, TAT, PAP, D-dimer, vWF, TF and TFPI plasma levels were determined by enzyme-linked immunosorbent assay (ELISA) method (Enzygnost F1 + 2, Enzygnost TAT and Enzygnost PAP; Behringer, Marburg, Germany; D-Dimer test Gold; Agen, Brisbane, Australia; vWF; BioMérieux, Marcy l'Etoile, France; IMUBIND Tissue Factor ELISA Kit and

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IMUBIND Total TFPI ELISA Kit; American Diagnostica Inc, Greenwich, Connecticut, USA).

To determine plasma homocysteine, venous blood was collected in tubes containing 0.17 mol/l ethylenediaminoacetate, immediately put in ice and centrifuged within 30 min at 4°C (1500 × *g* for 15 min). The supernatant was stored in aliquots at −80°C until assay. The plasma levels of total homocysteine (free and protein bound) were determined by fluorescence polarization immunoassay (IMX Abbott Laboratories, Oslo, Norway). Hyperhomocysteinaemia was diagnosed when fasting plasma levels exceeded the 95th percentiles of the distribution of values obtained in controls. All data were corrected for haematocrit.

Factor V (FV) Leiden and factor II (FII G20210A) gene mutations were analysed as previously described [27,28]. Briefly, the FV Leiden mutation was amplified using as forward primer 5′-ACC CAC AGA AAA TGA TGC CCA G-3′ and as reverse primer 5′-TGC CCC ATT ATT TAG CCA GGA G-3′ (Pharmacia Biotech, Milan, Italy). Twenty microlitres of the 223 amplified products were digested with *Mnl*I (New England Biolabs, Beverly, Massachusetts, USA) for 4 h at 37°C with 1 U enzyme per reaction. Digestion of normal allele [223 base pairs (bp)] produced fragments of 37, 82, and 104 bp, whereas digestion of mutated allele produced fragments of 37 and 141 bp.

The DNA sequence spanning the FII G2021A polymorphism was amplified by polymerase chain reaction using the primer 5′-TCT AGA AAC AGT TGC CTG GC-3′ and the mutagenic primer 5′-ATA GCA CTG GGA GCA TTG AAG C-3′. The more frequent allele lacks the restriction site and therefore generates only a 345 bp fragment by *Hind*III (Pharmacia Biotech) polymerase chain reaction digestion, whereas digestion of mutated allele produced fragments of 322 and 23 bp.

FV Leiden and FII G20210A digestion products were electrophoresed on 3% agarose gel (Pharmacia Biotech) and on 8% polyacrylamide gel (Pharmacia Biotech), respectively, and were visualized by ethidium bromide staining.

Statistical analysis

The data are presented as median and range. The non-parametric Kruskal–Wallis test followed by the *post-hoc* test were used for multiple comparisons between single groups. Spearman's rank correlation coefficient was used for the correlation analysis.

The results were considered statistically significant at $P < 0.05$.

Results

Data of blood haemostatic parameters in patients and controls are reported in Table 1. In patients with severe OHSS, D-dimer, TAT, F1 + 2, PAP, and vWF plasma levels were significantly higher than those observed both in the case–control group and in healthy controls (Table 1). D-Dimer levels exceed the 95th percentile of healthy controls in 20/25, TAT in 21/25 and F1 + 2 in 14/25 OHSS patients.

In severe OHSS patients, TF levels were higher ($P < 0.05$) and TFPI levels were lower ($P < 0.005$) than those found in both case–controls and healthy controls.

No significant differences in all blood haemostatic parameters between case–control group and healthy controls were observed (Table 1).

TAT levels related with D-dimer, PAP and vWF ($r = 0.54$, $P < 0.0001$, $r = 0.59$, $P < 0.0001$ and $r = 0.32$, $P < 0.001$, respectively). D-Dimer values were related with serum E_2 levels and oocyte number recovered ($r = 0.45$, $P < 0.01$ and $r = 0.47$, $P < 0.001$, respectively). Significant relationships were also observed between TFPI and vWF levels ($r = -0.37$,

Table 1 Blood haemostatic parameters in patients with ovarian hyperstimulation syndrome (OHSS) and in control subjects

	OHSS ($n = 25$)		Case–controls ($n = 25$)		Healthy controls ($n = 25$)		
	Median	Range	Median	Range	Median	Range	*P* value
D-Dimer (ng/ml)	188.0	(29–1449)	36.0	(2–252)	32.0	(2–124)	< 0.0001*, < 0.0001†
TAT (μg/l)	7.2	(1.0–82.6)	3.0	(1.7–46.5)	1.9	(0.7–7.5)	< 0.05*, < 0.01†
F1 + 2 (nmol/l)	1.8	(0.6–10.0)	0.8	(0.3–2.3)	1.0	(0.6–1.9)	< 0.01*, < 0.01†
TF (pg/ml)	108.0	(41–383)	78.6	(21.6–131.6)	75.0	(36.4–92)	< 0.05*, < 0.01†
TFPI (ng/ml)	41.4	(18–64.8)	60.0	(28.0–104)	51.0	(34.8–167)	< 0.01*, < 0.01†
PAP (μg/l)	1423.0	(354–3164)	873.0	(482–1028)	400.0	(137–1017)	< 0.0001*, < 0.0001†
vWF (%)	178.0	(87–297)	121.0	(66–210)	106.0	(64–182)	< 0.001*, < 0.001†

TAT, thrombin–antithrombin complex; F1 + 2, prothrombin fragment F1 + 2; TF, Tissue factor; TFPI, tissue factor pathway inhibitor; PAP, plasmin–antiplasmin complex; vWF, von Willebrand factor. *OHSS patients versus healthy controls, †OHSS patients versus case–controls.

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$P < 0.01$), TFPI and PAP ($r = -0.30$, $P < 0.01$) and TF and TAT ($r = 0.32$, $P < 0.01$).

D-Dimer and TAT levels were also related to the outcome of pregnancy (Table 2): actually, they were significantly ($P < 0.05$ and $P < 0.005$, respectively) higher in OHSS patients with unsuccessful pregnancy with respect to those with successful pregnancy outcome.

In the case–control group, no significant differences between patients with unsuccessful and successful outcome were found (data not shown).

In no patients were protein C, protein S and antithrombin levels out of the range of controls (data not shown).

The FII G20210A mutation was found in three OHSS patients; the FV Leiden G16191A mutation was found in one OHSS patient and in two case–control subjects, and mild hyperhomocysteinaemia in two OHSS patients and in one case–control subject.

All three women with the FII G20210A mutation had an unsuccessful outcome, whereas the outcome was successful in the women with the FV Leiden G16191A mutation and in those with mild hyperhomocysteinaemia.

Discussion

Marked alterations in the haemostatic system have been documented in COH and in severe OHSS [14,16,17,29]. In this study, clotting activation has been observed in severe OHSS patients as documented by increased levels of F1 + 2, TAT and D-dimer. Increased thrombin formation and fibrin degradation was related with high oestrogenaemia, indicating that the prothrombotic state is probably a consequence rather than an intrinsic aspect of the pathophysiology of OHSS. Furthermore, in the group of women undergoing IVF who did not develop OHSS, we did not observe any significant difference in comparison with the healthy control group. Therefore, the marked hypercoagulability observed in OHSS patients seems to probably be associated with the development of OHSS rather than the process of IVF. Interestingly, the present study shows that hypercoagulability was more marked in women in whom the outcome of the IVF-ET was unsuccessful. This suggests a role of hypercoagulability in the occurrence of some severe OHSS complications and supports the concept that these women are at high risk for thrombotic events. The lack of significant association in women undergoing IVF, but who do not develop OHSS between blood clotting activation markers and outcome suggests that they could have a role only in conditions in which severe complications occurs. Antithrombotic prophylaxis is not widely employed in relation to the possible occurrence of severe OHSS. Therefore, from a clinical point of view, the relation of D-dimer levels with clinical outcome suggests a possible usefulness of monitoring this parameter in women undergoing COH. However, the hypothesis of a predictive role of D-dimer for the outcome of pregnancy should be assessed by *ad hoc* studies.

This study is the first report showing a significant reduction of plasma TFPI, in addition to an increase of TF plasma levels in severe OHSS patients. TFPI is an important regulator of the extrinsic blood coagulation and significantly contributes to the anticoagulant properties of the endothelium [25,30]. TFPI decrease has been reported in conditions in which blood clotting activation occurs [30–32]. The low levels of TFPI observed in severe OHSS patients might be related to a reduced hepatic synthesis because low levels of TFPI have been reported in liver disease [33]. However, in our patients the concentration of proteins, such as fibrinogen or prothrombin complex factors or coagulation physiologic inhibitors, were in the normal range, so making unlikely a relevant defect in liver protein synthesis in these patients. As plasma TFPI is derived

Table 2 Blood haemostatic parameters related to outcome of pregnancy

	Outcome of pregnancy				
	Successful ($n = 11$)		Unsuccessful ($n = 14$)		
	Median	Range	Median	Range	P
D-Dimer (ng/ml)	145.0	29–330	226.5	56–1449	< 0.05
TAT (μg/l)	5.0	1–19.6	19.8	3.1–82.6	< 0.005
F1 + 2 (nmol/l)	1.5	0.6–2.5	1.9	0.6–10.0	ns
TF (pg/ml)	91.0	41–192	119.0	49.4–383	ns
TFPI (ng/ml)	32.0	18–53.6	42.9	21–64.8	ns
PAP (μg/l)	1369.0	1007–1808	1682.0	354–3164	ns
vWF (%)	190.0	115–297	146.0	87–259	ns

TAT, thrombin–antithrombin complex; F1 + 2, prothrombin fragment F1 + 2; TFPI, tissue factor pathway inhibitor; PAP, plasmin–antiplasmin complex; vWF, von Willebrand factor; ns, not significant.

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mainly from vascular endothelial cells [34], low levels of plasma TFPI may rather reflect either an endothelial dysfunction with impaired TFPI synthesis and secretion or a chronic depletion of the TFPI endothelial pool [35–37]. Accordingly, in this study the decrease in TFPI was related to an increase in vWF levels, suggesting that TFPI exhaustion was associated with endothelial injury. Moreover, the negative relationship between TFPI and plasmin formation (assessed by PAP complex levels), may indicate an increased endothelial t-PA release in severe OHSS patients.

Previous investigations showed increased TF production by monocytes from severe OHSS patients [38,39], but no data were available about TF levels in plasma. In our study, we have demonstrated for the first time that TF plasma levels are increased in severe OHSS, possibly by its release from activated monocyte/macrophages and/or vascular endothelial cells. The presence of high TF in plasma may, in turn, contribute to trigger blood clotting activation as indicated by the correlation with TAT. In severe OHSS patients, monocytes and endothelial cells may be activated or injured by several mediators. Actually, cytokines and growth factors, whose increased concentrations have been documented in this clinical condition [40,41], are able to cause enhanced TF synthesis and release [42].

In addition to these stimulators, the renin–angiotensin system may be involved. In experimental animals, angiotensin II was found to play a role in the development of weight gain, third space fluid accumulation and intravascular fluid depletion in OHSS, and angiotensin-converting enzyme (ACE) inhibition resulted in a 40% decrease in the incidence of OHSS [43]. An increased ACE activity was described to be associated with the development of OHSS in a clinical report [10]. Furthermore, ACE modulates TF synthesis in monocytes and ACE inhibitors reduce TF in both *in vitro* and *in vivo* studies [44,45].

In our patients the prevalence of the FII G20210A mutation was higher than both in controls and in our laboratory reference group (3% in more than 400 subjects) and, most importantly, it was associated with negative outcome; however, the limited number of patients does not allow any further comment.

In conclusion, this study documents the correlation between the magnitude of ovarian stimulation and hypercoagulability and the involvement of the TF–TFPI complex as possible expression of endothelial dysfunction and monocyte activation in severe OHSS. Further investigations on a large number of patients are needed to determine the possible role of markers of blood clotting activation for the clinical management of these patients.

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