Haematocrit, leukocyte and platelet counts and the severity of the ovarian hyperstimulation syndrome

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Previous studies have shown that severe ovarian hyperstimulation syndrome (OHSS) is secondary to circulatory dysfunction due to the simultaneous occurrence of increased vascular permeability and marked arteriolar vasodilatation which lead to an intense homeostatic stimulation of the renin–aldosterone and sympathetic nervous systems and antidiuretic hormone (ADH). In the present report, we have investigated the correlation between changes in haematocrit concentration, and white blood cell (WBC) and platelet counts and the severity of OHSS, as assessed by these markers of effective intra-arterial blood volume, in a series of 50 patients. In comparison with recovery values (4–5 weeks after hospital discharge), OHSS patients showed arterial hypotension, tachycardia, oliguria, very high plasma concentrations of renin, aldosterone, norepinephrine and ADH, and increased mean haematocrit values and WBC and platelet counts. The haematocrit concentration values were directly related to the plasma concentrations of vasoactive substances (plasma renin activity, aldosterone, norepinephrine and ADH) during OHSS (P < 0.001). In contrast, no correlation was evident between WBC or platelet counts, and the severity of OHSS, as assessed by these markers of effective intra-arterial blood volume, in a large series of patients.

Introduction

Severe ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening post-ovulatory complication of ovulation induction. The syndrome has been extensively studied during the last decade due to the increasing numbers of women receiving various ovarian stimulation protocols as part of different infertility treatments.

Severe OHSS is characterized by two major components: the first is sudden bilateral ovarian enlargement and the second is an acute shift of intravascular fluid into the third space (Pride et al., 1990; Rizk and Aboulghar, 1991). However, the pathogenesis of the condition is unclear. Traditionally, severe OHSS has been attributed to an increased vascular permeability induced by an unknown substance synthesized by the enlarged ovaries (Lancet, 1991; Rizk and Aboulghar, 1991). On the basis that intravascular depletion would be the main pathophysiological event, haematocrit concentration has been considered to be the best indicator of severity in the syndrome (Bergh and Navot, 1992; Navot et al., 1992). Thus, haematocrit and the white blood cell (WBC) count have been proposed as the prime parameters indicative of the severity of OHSS (Navot et al., 1996).

We have recently reported that, in addition to increased capillary permeability and the escape of fluid to extravascular spaces, severe OHSS is consistently associated with marked arteriolar vasodilation. The simultaneous occurrence of both disorders leads to a decrease of fluid in the arterial vascular compartment and arterial hypotension which cause an intense homeostatic stimulation of the renin–aldosterone and sympathetic nervous systems and antidiuretic hormone (ADH) to maintain an effective arterial blood volume (Balasch et al., 1991, 1994, 1995).

We report here the results of a study investigating the relationship between changes in haematocrit concentration, and WBC and platelet counts, and the severity of OHSS, as assessed by those markers of effective intra-arterial blood volume, in a large series of patients.

Materials and methods

Our study included 50 consecutive patients, who were admitted to our hospital for severe OHSS according to the classification proposed by Golan et al. (1989). Of these patients, 10 were referred from other centres. Multiple follicular growth had been induced with gonadotrophin-releasing hormone agonist/gonadotrophin treatment for in-vitro fertilization (IVF; n = 44) or gonadotrophin-induced ovulation for anovulatory infertility (n = 6). In all, 21 women had polycystic ovarian syndrome, a condition predisposing to OHSS (Navot et al., 1996). Consecutive IVF patients (n = 10) from our centre, who were seen within 1 week of the embryo transfer (in the midluteal phase of the IVF cycle) were used as controls. These women, who had no clinical or ultrasonographic evidence of ascites, presented with abdominal discomfort and had mild OHSS (ovarian
enlargement <6 cm diameter due to gonadotrophin treatment). All patients gave informed consent to participate in the study which was approved by the Investigation and Ethics Committee of our hospital.

After diagnosis of severe OHSS, patients were hospitalized for bed rest and strict clinical, biochemical, haematological, and haemodynamic monitoring and given a 60 mEq sodium diet. The next morning, after overnight fasting from food and after 2 h of bed rest, arterial blood pressure and heart rate were measured and an antecubital vein was catheterized. After 30 min, blood samples were taken to measure plasma renin activity, plasma aldosterone, norepinephrine, and ADH concentrations, and pertinent haematological and biochemical parameters. Patients were then confined to bed rest and given low-sodium diets. We added diuretics (furosemide, Seguril; Hoechst Forma, Barcelona, Spain; 20 mg given i.v. every 8–12 h) and plasma volume expansion with albumin (50 g/day of reduced salt albumin) for those patients with urine volume of <20 ml/h or sodium excretion of <20 mEq/day (Balasch et al., 1996a). No patient was treated with paracentesis. The women were readmitted 4–5 weeks after being discharged to repeat all these measurements, and thus each patient acted as her own control for neurohormonal and humoral studies during the syndrome. During the second study, 20 patients were pregnant and 15 carried successfully to term. However, neurohormonal and haematological parameters in these cases were similar to those of non-pregnant women. All non-pregnant women had the second evaluation during the follicular phase of their menstrual cycles.

Neurohormonal factors such as plasma renin activity, plasma concentrations of aldosterone, norepinephrine and ADH were measured by radioimmunoassay or radioenzymatic assay as previously reported (Balasch et al., 1991, 1994, 1995). Mean arterial pressure was calculated as diastolic blood pressure plus one third of the difference between the systolic and diastolic blood pressures.

Results are presented as mean ± SEM. The paired Student’s t-test and the Pearson bivariate method were used for statistical analysis. Both absolute values and percentage changes in haematocrit, and WBC and platelet counts during OHSS relative to baseline recovery values were used to calculate correlations between these parameters and absolute values and percentage changes in neurohormonal measurements (plasma renin activity, and aldosterone, norepinephrine, and ADH concentrations).

Results
The mean patient age was 31.4 years (range 26–37 years). Peak plasma oestradiol concentrations during ovarian stimulation in the 50 patients studied were 4502 ± 334 pg/ml (range 1826–8125 pg/ml). The mean number of follicles observed by vaginal ultrasonography on the day of human chorionic gonadotrophin administration was 28.6 ± 1.3 (range 12–35). At admission to hospital, the size of the ovaries ranged between 12×13 and 19×20 cm, and all patients had marked abdominal distension because of the presence of enlarged ovaries and ascites. The amount of fluid retained, as estimated by the loss of body weight during hospitalization, was 3.3 kg (range 1.9–4.2 kg). Compared with recovery values, patients showed arterial hypotension, tachycardia, oliguria and very high plasma concentrations of renin, aldosterone, norepinephrine and ADH (Table I). The serum creatinine concentration was normal in all patients (upper normal limit in our laboratory, 1.2 mg/dl) but this parameter was significantly higher during the syndrome than after recovery, thus suggesting a small decrease in the glomerular filtration rate (Table I).

Mean haematocrit values and leukocyte and platelet counts were increased significantly during OHSS (P < 0.001). Statistical correlations between haematological variables and neurohormonal factors were calculated. Correlation coefficients and probabilities (P) for plasma renin activity, and aldosterone, norepinephrine and ADH concentrations and three variables, haematocrit, WBC and platelet counts are presented in Table II. No correlation was evident between either absolute values during severe OHSS or percentage changes during the syndrome relative to baseline recovery values in WBC or platelet counts and absolute values or percentage changes in plasma renin activity, aldosterone, norepinephrine, and ADH. In contrast, both percentage changes in haematocrit concentration or absolute haematocrit values during the syndrome correlated directly with either absolute values or percentage changes observed in those neurohormonal measurements (Table II). Haemoconcentration during OHSS, arbitrarily defined as a haematocrit concentration >10% over baseline recovery values, developed in 30 (60%) patients. Table III shows neurohormonal and haematological measurements during OHSS in patients with and without haemoconcentration. Both absolute values and percentage changes in plasma renin activity, and plasma aldosterone, norepinephrine, and ADH concentra-
Table II. Correlation between haematocrit, white blood cell (WBC) and platelet counts and neurohormonal measurements in 50 patients with severe ovarian hyperstimulation syndrome (OHSS). Figures are correlation coefficients with probabilities shown in parentheses

<table>
<thead>
<tr>
<th>Haematological Parameters</th>
<th>Plasma renin activity</th>
<th>Aldosterone</th>
<th>Norepinephrine</th>
<th>Antidiuretic hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute value</td>
<td>Percentage increment</td>
<td>Absolute value</td>
<td>Percentage increment</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.44 (0.002)</td>
<td>0.46 (0.002)</td>
<td>0.46 (0.002)</td>
<td>0.51 (0.001)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>0.11 (0.2)</td>
<td>0.03 (0.5)</td>
<td>0.04 (0.6)</td>
<td>0.02 (0.5)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.18 (0.2)</td>
<td>0.04 (0.6)</td>
<td>0.07 (0.6)</td>
<td>0.02 (0.5)</td>
</tr>
</tbody>
</table>

Table III. Neurohormonal and haematological measurements during severe ovarian hyperstimulation syndrome (OHSS) in patients with and without haemoconcentration. Values given are mean ± SEM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Haemoconcentration (n = 30)</th>
<th>No haemoconcentration (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit Absolute value</td>
<td>46.9 ± 0.82</td>
<td>41.05 ± 0.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Percentage increment</td>
<td>24.62 ± 1.91</td>
<td>3.91 ± 1.09</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>65.9 ± 9.2</td>
<td>38.4 ± 7.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Absolute value</td>
<td>8137.5 ± 1118</td>
<td>6240 ± 1520</td>
<td>0.01</td>
</tr>
<tr>
<td>Percentage increment</td>
<td>265.1 ± 25.3</td>
<td>175.1 ± 19</td>
<td>0.02</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>1737.4 ± 201</td>
<td>1053.3 ± 150.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Absolute value</td>
<td>698.2 ± 65.2</td>
<td>460.7 ± 37.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Percentage increment</td>
<td>250.9 ± 30.8</td>
<td>127.9 ± 25.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma antidiuretic hormone (pg/ml)</td>
<td>6.1 ± 1.1</td>
<td>3.1 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Absolute value</td>
<td>573.1 ± 126.9</td>
<td>196.7 ± 4.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Percentage increment</td>
<td>16 938 ± 773</td>
<td>14 012 ± 979</td>
<td>0.01</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>203.8 ± 16.0</td>
<td>161.6 ± 14.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Absolute count</td>
<td>361 433 ± 16 907</td>
<td>338 473 ± 21 925</td>
<td>0.3</td>
</tr>
<tr>
<td>Percentage increment</td>
<td>75.3 ± 8.3</td>
<td>66.1 ± 10.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table IV. Correlation between haematocrit, white blood cell (WBC) and platelet counts and neurohormonal measurements in 50 patients with severe ovarian hyperstimulation syndrome (OHSS). Figures are correlation coefficients with probabilities shown in parentheses

Table V. Neurohormonal and haematological measurements during severe ovarian hyperstimulation syndrome (OHSS) in patients with and without haemoconcentration. Values given are mean ± SEM

Discussion

OHSS is secondary to a circulatory dysfunction due to the simultaneous occurrence of increased vascular permeability and marked arteriolar vasodilation which lead to ascites formation, arterial hypotension, tachycardia, increased cardiac output, reduced peripheral vascular resistance, marked stimulation of the renin–angiotensin and sympathetic nervous systems and ADH, haemoconcentration, oliguria, sodium retention, hyponatraemia, and in extreme cases, renal failure and thrombotic events (Schenker and Weinstein, 1978; Golan et al., 1989; Lancet, 1991; Rizk and Aboulghar, 1991; Balasch et al., 1994; Dourron and Williams, 1996; Elchalal and Schenker, 1997). The presence of ascites, pleural effusion and even peripheral oedema, and the development of haemoconcentration with increased haematocrit have been the main arguments to support the contention that increased capillary permeability, mainly of
the ovarian vessels, is the pathogenic mechanism of severe OHSS (Schenker and Weinstein, 1978; Rizk and Aboulghar, 1991; Elchalal and Schenker, 1997). The high plasma concentrations of renin subsequently observed in severe OHSS were also considered to be of ovarian origin since both mature ovarian follicles and the corpus luteum are capable of synthesizing renin (Bergh and Navot, 1992; Douron and Williams, 1996; Elchalal and Schenker, 1997). According to this pathogenic hypothesis, the occurrence of thromboembolic phenomena has been related to the rapid body fluid shift leading to haemoconcentration and increased blood viscosity (Schenker and Weinstein, 1978; Rizk and Aboulghar, 1991; Elchalal and Schenker, 1997).

On the basis of the above pathogenic hypothesis, the haematocrit, and also the WBC count (as an additional measure of haemoconcentration), have been proposed as markers of severity in the clinical assessment of OHSS (Bergh and Navot, 1992; Navot et al., 1996). However, no objective data have been reported to support this contention. Recent studies from our group have shown that the pathogenesis of severe OHSS is more complex than currently understood and marked peripheral arteriolar vasodilatation is a major event in the development of the syndrome (Balasch et al., 1991, 1994, 1995). These patients present a hyperdynamic circulation characterized by arterial hypotension, high cardiac output and low peripheral vascular resistance, thus indicating the existence of peripheral arteriolar vasodilatation. In addition, the increased activity of the renin–angiotensin–aldosterone system in this condition is associated with a marked stimulation of other endogenous vasoactive mechanisms, such as the sympathetic nervous system and ADH, thus indicating that renin–aldosterone system hyperactivity is a component of a generalized homeostatic response to maintain circulatory function rather than a primary ovarian event. The increased activity of the renin–angiotensin and sympathetic nervous systems and the high plasma concentrations of ADH, which are sensitive markers of effective intra-arterial blood volume, would counteract an unknown vasodilator mechanism, thus maintaining arterial pressure within normal or near normal limits.

On the basis of these new pathophysiological data, the present study objectively shows that haematocrit is a marker of severity in OHSS, a feature previously suggested by us (Balasch et al., 1994). This is supported by two facts. Firstly, a direct correlation was found between haematocrit and neuro-hormonal measurements irrespective of considering absolute values or percentage changes during OHSS relative to baseline recovery values. Secondly, patients with increased haematocrit concentration had the highest absolute values and percentage increment in plasma concentrations of renin, aldosterone, norepinephrine, and ADH. In this latter group of patients a greater reduction of fluid in the arterial vessels would lead to a more intense activation of the endogenous vasoconstrictor systems.

Neither leukocyte nor platelet counts correlated with the severity of the OHSS in the present study despite the observation that both were significantly increased during the syndrome. Stress-induced changes in blood leukocyte number are well known (Dhabhar et al., 1996) and leukocytosis during severe OHSS may to some extent be attributed to a generalized stress reaction. Similarly, secondary or reactive thrombocytosis is observed in a number of clinical circumstances, including acute and chronic inflammatory disorders, malignancy, following surgery, and several other stress situations (Burstein and Harker, 1983; Hollen et al., 1991). In fact, characteristics of the severe OHSS resemble a non-infectious systemic inflammatory response, because both share the same clinical manifestations (Dinarello et al., 1993; Loret de Mola et al., 1996a).

It is important to note, however, that the production of blood leukocytes and their numbers in circulation are regulated by complex interactions involving endogenous haematopoietic cytokines and interleukins (Quesenberry, 1995; Hock et al., 1997). Recently, it has been reported that an increase in WBC numbers may develop both in patients having severe OHSS and in the luteal phase of women undergoing ovulation induction, and a correlation was found between the WBC count increase and plasma concentrations of interleukin-6 (Abramov et al., 1996) and granulocyte-colony stimulating factor (Hock et al., 1997). However, leukocytosis was more pronounced in patients developing OHSS as in our own findings and those reported by Abramov et al. (1996) than in women receiving exogenous gonadotrophins for controlled ovarian stimulation. Interestingly, Loret de Mola et al. (1996a) indicated that interleukin-6 concentrations are higher in women undergoing ovarian stimulation, irrespective of developing OHSS, than in unstimulated controls but cytokine serum concentrations in this later group were significantly lower than after controlled ovarian hyperstimulation. Therefore, a plausible explanation for increased WBC counts during ovulation induction and OHSS is that menotrophins may stimulate follicular cells to secrete more cytokines which in turn would increase the production of leukocytes. The magnitude of increase in leukocyte number will depend on the degree of (hyper)stimulation of the patient.

Increased platelet count has been traditionally considered as a feature of severe OHSS which, together with other altered coagulation factors, and in combination with the hyperviscosity (haemoconcentration) would lead to intravascular thrombosis, an extreme clinical manifestation of the syndrome (Schenker and Weinstein, 1978; Pride et al., 1990). However, changes in coagulation parameters have been correlated neither with oestrogen nor the haematocrit (Pride et al., 1990) and a recent report (Kodama et al., 1995) indicated that platelet count is not a blood haemostatic marker of thromboembolism in OHSS patients. This is in agreement with findings in the present study showing that platelet count is not a marker of severity in the syndrome. In fact, severe thrombotic events after ovulation induction recently have been reported in women without any concomitant clinical sign of OHSS (Aurousseau et al., 1995) and the occurrence of thromboembolic events in patients with severe OHSS may involve some specific factors having procoagulant activity (Balasch et al., 1996b). Elevated concentrations of interleukins, e.g. interleukin-6, interleukin-1, and tumour necrosis factor have been reported during OHSS and/or controlled ovarian hyperstimulation (Loret de Mola et al., 1996a,b; Hock et al., 1997; Rizk et al., 1997), and are
associated with reactive thrombocytosis. Therefore, this may explain the increased platelet counts found in our patients.

In conclusion, the present study shows that haematocrit is a biological marker of the severity of OHSS as indicated by plasma measurement of volume-dependent endogenous vasoactive substances. In contrast, increased WBC and platelet counts are not correlated with neurohormonal measurements in the syndrome and may be attributed to a generalized stress reaction and/or elevated cytokine production by the stimulated ovaries.

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