Serum concentration of vascular endothelial growth factor cannot predict the course of severe ovarian hyperstimulation syndrome

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Vascular endothelial growth factor (VEGF) is stated to be a possible promoter of the development and the severity of ovarian hyperstimulation syndrome (OHSS). The secretion of VEGF in granulosa cells seems to be human chorionic gonadotrophin (HCG) dependent. In this prospective study, the data of 10 patients suffering from severe OHSS with ascites and pleural effusions (haematocrit, fluid balance, serum HCG, serum oestradiol) were analysed. The serum VEGF concentration declined during the period of clinical improvement but provided no additional diagnostic information for the further course of OHSS. VEGF was neither an early marker of improvement, nor of worsening of the clinical picture of the OHSS. Serum oestradiol concentrations and serum VEGF concentrations showed a statistical correlation ($r = 0.33, P < 0.001$). There was no correlation between haematocrit and VEGF, nor between serum HCG and VEGF. To conclude, although VEGF may be involved in the pathogenesis of OHSS, it is not an important clinical marker for the course of an OHSS.

Key words: VEGF/OHSS

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a severe complication of controlled ovarian hyperstimulation, which can lead to life-threatening complications including thromboembolic events and even death (Schenker and Ezra, 1994). The exact factors responsible for the clinical features of OHSS are not known.

Vascular endothelial growth factor (VEGF) is a heparin-binding glycoprotein with vascular permeability-enhancing, angiogenic and endothelial cell-specific mitogenic activities (Ferrara et al., 1991). Some authors have suggested that VEGF may be responsible for several features of the OHSS (McClure et al., 1994; Robertson et al., 1995; Neulen et al., 1995), because VEGF increases vascular permeability, which may explain fluid leakage in the third space. This leakage is responsible for the development of ascites, pleural effusions, oedema and haemoconcentration. Elchalal and Schenker (1997) have concluded in a recent review that, according to the results shown in the literature, VEGF has a major role in the pathogenesis of OHSS. It is not known, however, whether measurements of circulating VEGF can give additional information on the clinical course of OHSS and predict the improvement of the clinical features.

We therefore prospectively analysed the data set of 10 patients with severe OHSS.

Materials and methods

Stimulation schemes and definition of OHSS

Ten consecutive patients, who presented symptoms of severe OHSS (grade III) according to the WHO criteria (1973), were included in this prospective clinical study. All patients presented with ascites and pleural effusions, and were hospitalized. They were treated for male factor infertility with in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and were stimulated after hormonal suppression with a gonadotrophin-releasing hormone (GnRH) analogue in the long protocol. For luteal phase support the patients received 600 mg micronized progesterone daily. No patients had endocrinological diseases or suffered from polycystic ovary syndrome.

Beginning on the day of admission, all patients were treated with large amounts of i.v. fluid (Ringer’s lactate, maximally 50 ml/kg body weight/day). All patients received low molecular weight heparin (Fragmin P®; Pharmacia, Erlangen, Germany) subcutaneously. Fluid balance, body weight, haematocrit and serum VEGF concentration were determined daily. Human chorionic gonadotrophin (HCG) was not measured until day 9 post oocyte retrieval.

Measurement of VEGF

The VEGF (isoform 165) was measured in serum using the Quantikine® VEGF DV O0 ELISA (DPC Biermann, Wiesbaden, Germany). The immobilized antibody was monoclonal, while the second horseradish peroxidase-conjugated antibody was polyclonal. The intra- and interassay coefficients of variance were 5% and 7.5%, respectively. The lower detection limit was 9 pg/ml. Assay characteristics have been reported previously (Heits et al., 1997).

Statistics

Pearson’s correlation coefficient was calculated to determine if there was a statistical relationship between two variables.

Results

The mean oestradiol concentration on the day of HCG administration for ovulation induction was 3267 pg/ml (range: 1394–6923), the mean number of oocytes retrieved was 12.4 (range: 9–20). The patients were hospitalized for a mean of 7.55 (range: 4–11) days. Five patients became pregnant. Three singleton, one twin and one triplet ongoing pregnancy were achieved.

The VEGF serum concentrations ranged from 50–780 pg/ml. The serum oestradiol concentrations during the late stimulation

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phase and the luteal phase were correlated with the serum VEGF concentration. The correlation coefficient was $r = 0.33$ ($P < 0.001$). There was no correlation between haematocrit and VEGF serum concentrations ($r = 0.28$, $P = 0.072$) or between HCG and VEGF serum concentrations ($r = 0.025$, $P = 0.84$). The VEGF serum concentrations on the day of admittance and on the day of significant clinical improvement were not different.

Figure 1 shows the laboratory and clinical data from two patients with OHSS who became pregnant after the treatment.

In no patient was the decrease or rise of the serum VEGF concentration a better predictor than classical parameters like haematocrit, fluid balance or clinical symptoms.

**Discussion**

The pathogenesis of OHSS and the associated increase in vascular permeability is not fully understood. Several substances have been thought to be involved in the pathogenesis of OHSS, including histamine, interleukins, endothelin 1 and
VEGF (Elchalal and Schenker, 1997). Yan et al. (1993) have shown that VEGF messenger RNA (mRNA) is produced in luteinized granulosa cells. High amounts of VEGF were also detected in follicular fluid (Krasnow et al., 1996). McLaren et al. (1994) have proposed that VEGF might be the major capillary permeability agent in OHSS ascitic fluid. Neulen et al. (1995) demonstrated in vitro that the VEGF mRNA concentration in luteinized granulosa cells can be increased by the addition of HCG. These results were confirmed by Robertson et al. (1995) in vivo. Only a poor correlation of urine VEGF:creatinine ratios with plasma oestradiol was described (Robertson et al., 1995).

Abramov et al. (1997) reported recently that in seven patients suffering from OHSS the serum VEGF concentrations were higher compared to those in a control group without OHSS. The serum VEGF values decreased significantly after clinical convalescence. We cannot confirm this observation, however: the VEGF levels in our study were similar when the day of admittance and the day of clinical improvement were compared. This may be due to a high number of patients suffering from a late onset OHSS (6/10), who had an increment of VEGF due to the endogenous HCG rise, concomitant to the improvement of the clinical picture. Abramov et al. (1997) gave no information on the type of OHSS in their patients.

Abramov et al. (1997) proposed a direct relationship between the serum VEGF concentrations and the clinical picture of OHSS, but gave no information as to whether the change in VEGF concentration preceded the improvement of the clinical picture.

In our study the serum concentration of VEGF was measured in conjunction with other, established laboratory and clinical parameters during the entire course of severe OHSS. It is believed that high oestradiol levels and a high haematocrit indicate a severe form of OHSS. We confirm that there may be a relationship between VEGF serum concentration and OHSS, since there was a positive correlation between VEGF and oestradiol concentrations. This is in accordance with the findings of other authors, who have described a cyclic pattern of VEGF in the peritoneal fluid of endometriosis patients (McLaren et al., 1996a), and the regulation of VEGF concentrations by ovarian steroids (McLaren et al., 1996b) or oestradiol and tamoxifen (Hyder et al., 1996).

Based on serum VEGF values, the course of the OHSS could not be predicted more efficiently than using haematocrit, fluid balance and the patients’ clinical picture.

There was a weak positive correlation between haematocrit and VEGF serum concentrations. However, this correlation is difficult to interpret, since all patients were treated with large volumes of i.v. fluid. We do not know if there is a genuine relationship between haematocrit and circulating VEGF, since it is impossible for medical and ethical reasons to withhold treatment for prevention of haematocrit increase with its higher thrombotic risk.

Neulen et al. (1995) and Robertson et al. (1995) showed that HCG triggered the production of VEGF by granulosa cells in vitro. The present study confirmed in vivo an initial rise of circulating VEGF concurrently with the rise of HCG. However, there was no correlation with HCG values up to the 6th week of gestation. Therefore, it can be concluded that HCG may induce VEGF production, but that other factors must also be involved.

We conclude that there is a relationship between the serum VEGF concentration and the development of an OHSS. However, other factors must contribute to the clinical features. These may explain why the elevated serum VEGF concentrations did not cause a worsening of the clinical picture when HCG rose, i.e. there was no occurrence of a late onset OHSS in our pregnant patients and no increased persistence of the OHSS when HCG levels increased further. A routinely performed measurement of serum VEGF during the course of an OHSS appears to be of little diagnostic value, since the clinical course cannot be predicted more precisely than with the traditional markers of OHSS including fluid balance, body weight and haematocrit.

References


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