Increased early pregnancy loss in IVF patients with severe ovarian hyperstimulation syndrome

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BACKGROUND: Since severe ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of assisted reproduction, the focus of attention in such cases is placed firmly upon the health of the patient, with the endeavour to achieve a pregnancy being considered of secondary importance. The aim of this study was to focus on the pregnancy rate and pregnancy outcome in IVF patients hospitalized for severe or critical OHSS, in one centre, during a period of 6 years. METHODS: We compared the characteristics of patients with severe OHSS: those who conceived with the ones who did not conceive, and among pregnant IVF patients, those with ongoing pregnancies with those that miscarried. RESULTS: Pregnancy was achieved in 60 of 104 (58%) patients with severe OHSS. Pregnancy continued until delivery in 37 of these 60 patients (62%), whereas the remaining 23 (38%) aborted. The pregnancy and abortion rates in patients with severe OHSS were significantly higher than those of IVF patients without OHSS, during the same time period [23% (1138/4922) and 15% (169/1138) respectively, \( P < 0.001 \)]. The mean duration of hospitalization for OHSS was significantly shorter in those who delivered compared with those who aborted (5.9 ± 3.2 versus 10.5 ± 9.6 days, \( P < 0.01 \)) and in the non-pregnant patients compared with the pregnant patients (5.2 ± 3.2 versus 7.6 ± 6.6 days, \( P < 0.02 \)). CONCLUSIONS: The clinical pregnancy rate of IVF patients with severe OHSS was significantly higher than that of patients without the syndrome. A longer stay in hospital—reflecting a more severe form of OHSS—was correlated with a higher frequency of abortions. OHSS, necessitating hospitalization, is a detrimental clinical situation not only for the mother but also for the developing pregnancy.

Key words: IVF/ovarian hyperstimulation syndrome(OHSS)/pregnancy loss/pregnancy outcome

Introduction

A number of studies, published over the past decade, have accurately described the complications of ovarian hyperstimulation syndrome (OHSS). The incidence of OHSS after assisted reproductive technology (ART) is higher compared with ovulation induction protocols, due to the widespread use of GnRH analogues in ART, associated with the administration of higher doses of gonadotrophins, and treatment of younger women for their male partner’s infertility (Golan et al., 1988).

Severe OHSS is characterized by increased vascular permeability and thus the shift of fluids from blood vessels to extravascular space. As such, it often requires hospitalization and in its critical form may require intensive care unit (Whelan III and Viahost, 2000).

Since severe OHSS is a potentially life-threatening, iatrogenic complication that can occur in an otherwise healthy young woman desiring fertility, much effort is made in order to prevent it (Edwards et al., 1996; Abramov et al., 1999; Forman, 1999; Egbase, 2000). Naturally in such an acute situation the endangering syndrome is the primary focus and the anticipated pregnancy is of secondary importance.

Pregnancy outcome in IVF patients with severe or critical OHSS has so far been reported in only one retrospective Israeli national multicentre study of IVF patients (Abramov et al., 1998). The aim of the present study was to analyse the pregnancy rate and outcome (abortions and deliveries) in IVF patients hospitalized for severe and critical OHSS, in a single institution, during a 6 year period. We compared the characteristics of pregnant and non-pregnant patients with severe OHSS, and in pregnant patients we compared those with ongoing pregnancies and those who aborted.

Materials and methods

Between January 1994 and December 1999, 121 patients were hospitalized for severe and critical OHSS after 4922 IVF treatment cycles (2.5%). Of the 121 admitted cases only two were hospitalized twice following two consecutive treatment cycles. In 17 patients (13%) embryo transfer was not performed because of: early onset OHSS (10 patients); no sperm available for fertilization (three patients) and failed fertilization or cleavage (four patients). Therefore, the study group consisted of 104 IVF patients who were suffering from OHSS in its most severe form, after embryo transfer.
An established classification system was used to stage OHSS (Golan et al., 1989). Severe OHSS was diagnosed when patients presented with massive ascites or hydrothorax along with prominent abdominal discomfort and difficult breathing. Changes in blood volume, haemocencentration (haematocrit >50%, white blood count >25 000 per mm³) and increased viscosity, coagulation disorders, reduced renal/liver perfusion and function were all included in the definition of severe OHSS. In the presence of thromboembolic phenomena, adult respiratory distress syndrome (ARDS) and/or acute renal failure a diagnosis of critical OHSS was made (Navot et al., 1992).

Controlled ovarian hyperstimulation (COH) was carried out by the administration of 3.75 mg triptorelin (Decapeptyl; Ferring, Malmo, Sweden) 2 weeks prior to individualized administration of menotrophins (Pergonal; Teva, Petah Tikva, Israel). Oocyte retrieval was performed by the vaginal route guided by ultrasound under general anaesthesia. Intracytoplasmic sperm injection (ICSI) was carried out in 81 of 104 patients (78%) according to a previously published methodology (Van Steirteghem et al., 1993). Fertilization was confirmed after 16–18 h by visualization of two distinct pronuclei. Cleavage was assessed 24 h later. Embryos were considered for transfer and were introduced into the uterine cavity 48–72 h after the ICSI procedure. Embryo transfer was performed with a Wallace catheter (Simcare, Lancing, Sussex, UK). Luteal supplementation consisted of either HCG administration, 2500 IU every third day for 10 days, or 15 mg progestosterone (Provera; Wyeth, Mariemont, Belgium) daily for 10 days starting 3 days after embryo transfer. HCG administration was performed by the vaginal route guided by ultrasound under general anaesthesia. Intracytoplasmic sperm injection (ICSI) was carried out by the vaginal route guided by ultrasound under general anaesthesia. Luteal supplementation consisted of either HCG administration, 2500 IU every third day for 10 days, or 15 mg progestosterone (Provera; Wyeth, Mariemont, Belgium) daily for 10 days starting 3 days after embryo transfer. HCG administration was performed by the vaginal route guided by ultrasound under general anaesthesia. Intracytoplasmic sperm injection (ICSI) was carried out by the vaginal route guided by ultrasound under general anaesthesia.

Pregnancy rate was calculated considering only clinical pregnancies, determined by the visualization of a gestational sac by transvaginal ultrasound 3–4 weeks after embryo transfer. Early abortion was defined as pregnancy loss that took place before 12 weeks gestation and a late abortion, after 12 and before 20 weeks gestation.

The age of the patients, cause and duration of infertility, day 3 basal serum FSH and LH values were assessed. Regarding the COH the following were taken into consideration: duration of treatment and number of menotrophin ampoules needed for hyperstimulation; hormonal profile (estradiol, progesterone); number of follicles; aspirated oocytes and the total number of developing and transferred embryos were compared and evaluated. Day 14 serum HCG levels, the mean interval from the day of embryo transfer and the day of admission and hospitalization duration were also shown.

None of the patients had polycystic ovarian syndrome (PCOS). The mean FSH and LH levels of cycle day 3 were 5.9 ± 2.9 IU/l and 7.2 ± 2.8 IU/l. Some of the patients had the appearance of polycystic ovaries under ultrasound examination, as may be found in high responding patients.

The pregnancy rate and outcome (abortions and deliveries) in IVF patients hospitalized for severe and critical OHSS were compared with the pregnancy rate and outcome of our all non-hospitalized IVF population during the same years. The characteristics of the patients with severe OHSS were recorded and compared with patients who did and did not conceive. Likewise, the characteristics of the patients who delivered were compared with those who aborted.

Patients' characteristics and COH protocols were analysed statistically using Student's t-test. Delivery and abortion rates were compared using χ² test. P < 0.05 was considered statistically significant.

Results

A prominent and consistent decline in the incidence of severe and critical OHSS cases after IVF was noted, from 6.4 to 1.5% over the last 3 years.

Pregnancy was achieved in 60 (58%) of 104 patients with severe OHSS. Pregnancy continued until delivery in 37 of the 60 (62%) patients, whereas 23 (38%) miscarried. Of the 23 abortions, 19 (83%) were early and four (17%) late abortions. The pregnancy and abortion rates of patients with severe OHSS were significantly higher than those of IVF patients without OHSS during the same period of time [23% (1138/4922) and 15% (169/1138) respectively, P < 0.001]. The ongoing pregnancy rate per cycle in patients with OHSS was significantly higher [37/121 (30.6%)] than that of patients without OHSS [969/4922 (20%)] (P < 0.004).

The mean (± SEM) age of patients with OHSS was slightly lower than that of IVF patients with no OHSS (28.4 ± 4.9 versus 35.2 ± 4.5 years). The mean duration of infertility was 4.0 ± 3.0 years, and 60% of patients presented with primary infertility. Indications for IVF in patients with OHSS were: male factor (78%); unexplained infertility (11%); mechanical infertility (8%) and ovulation disorders in the remaining 3% of patients. Indications for IVF in patients without OHSS were: male factor (60%); unexplained infertility (20%); mechanical infertility (14%) and ovulation disorders in 6% of patients.

Thromboembolic phenomena occurred in two cases: one patient with pulmonary embolism and the other one with right subclavian vein thrombosis. Both patients had no autoimmune pathology or thrombophilia. Right hydrothorax was the sole presenting symptom in two patients. In one of them a repeated right hydrothorax also occurred on her second subsequent treatment cycle (Friedler et al., 1998). Acute renal failure occurred in one patient who had anti-phospholipid antibody syndrome.

Severe ‘early’ OHSS was diagnosed in 100 patients, (defined as the onset of OHSS within 8 days of initial HCG exposure relating to ‘excessive’ preovulatory response to stimulation). ‘Late’ OHSS was diagnosed in four patients (defined as onset of OHSS after 14–16 days of HCG administration that depends on the occurrence of pregnancy) (Mathur et al., 2000).

The only significantly different parameter between conception cycles and non-conception cycles in patients with OHSS was serum estradiol concentrations 2 weeks after embryo transfer (2078 ± 1223 versus 306 ± 583 pg/ml, P < 0.01) and the duration of hospitalization (7.6 ± 6.6 versus 5.2 ± 3.2 days, P < 0.02, respectively), as shown in Table I.

The characteristics and reproductive performance of IVF conception cycles with severe OHSS are shown in Table II. The mean age, mean number of HMG ampoules utilised during the COH and treatment duration of IVF conception cycles with OHSS were significantly different when compared with IVF patients who did not incur severe OHSS (32.6 ± 3.9 years, 40.5 ± 14.2 ampoules and 11.5 ± 3.1 days, respectively). The estradiol values on HCG day were similar in those who delivered and those who aborted (3165 ± 2385 pg/ml and 3471 ± 2440 pg/ml). The mean duration of hospitalization for OHSS was significantly shorter in those who delivered compared with those who aborted (5.9 ± 3.2 and 10.5 ± 9.6 days, P < 0.01).

Discussion

Severe OHSS is an iatrogenic, potentially life-threatening complication and much effort has been invested to prevent it. This
is well reflected by the gradual decline in the incidence of hospitalization for OHSS in our patients, reported over time: from 6.4% in 1994 to 1.5% in the last 3 years. Previous studies have reported an incidence of severe OHSS, after IVF, of approximately 1% which might be even higher because of the tendency to under-report (Forman, 1999). This gradual reduction reflects a change in our concepts regarding the use of less aggressive protocols for COH and the change towards the use of progestagens instead of HCG for luteal support. We still aim to aspirate as many oocytes as possible in order to select and freeze ‘spare’/additional embryos—but not at the expense of our patients suffering from severe OHSS. Moreover, other strategies may be chosen such as: withholding embryo transfer (Ferraretti et al., 1999), reducing the number of embryos transferred and reduced dose and delaying (‘coasting’) of HCG administration before oocyte aspiration (Dhont et al., 1998; Fluker et al., 1999).

Since the age of the pregnant patients who were included in the study was lower than the average age of IVF patients, with a higher number of aspirated oocytes per cycle, it is logical that the pregnancy rate, in this selected group, was higher when compared with the pregnancy rates in our general service (58 versus 23% respectively), as also reported in another study (Enskog et al., 1999). Abramov et al. (1998) also found an increased pregnancy rate in a multicentre study of 142 severe OHSS patients compared with non-OHSS patients (73 and 14.4% respectively) (Abramov et al., 1998).

We found an increased early pregnancy loss in the IVF patients who developed severe OHSS (38%) compared with an average miscarriage rate of 15% in patients without OHSS. Chen et al. (1997) found a 26.6% miscarriage rate in OHSS patients as opposed to 17% in the control group (Chen et al., 1997). Other studies have found miscarriage rates of: 29.8% (Abramov et al., 1998); 28.6% (MacDouggall et al., 1992) and 40% (Schenker and Polishuk, 1976). In contradiction to these results, Mathur et al. (2000) did not find an increased miscarriage rate in 41 IVF/GIFT clinical pregnancies, complicated by moderate or severe OHSS, compared with 501 clinical pregnancies in which OHSS did not occur (12.1 versus 16.8% respectively) (Mathur et al., 2000).

High miscarriage rates, such as these—whether from one centre or many centres—should have a logical explanation. Several hypotheses have been suggested by a number of investigators to explain the high miscarriage rate after OHSS: excessively high endogenous estradiol levels (Simon et al., 1998); abnormal cytokine levels (Abramov et al., 1996); excessive renin-angiotensin activation (Morris et al., 1995; De Nuccio et al., 1999) and by prostaglandins/histamines (Knox et al., 1975; Schenker and Polishuk, 1976) as the agents that may affect early pregnancy in patients with severe OHSS. The hypothesis regarding high endogenous estradiol levels that may harm early pregnancy was not supported by our data: the estradiol levels on the HCG day were similar in those patients with OHSS who delivered and those who aborted (3165 ± 2385 pg/ml versus 3471 ± 2440 pg/ml respectively). A trend for higher estradiol levels was found in those patients with OHSS that conceived compared with OHSS patients who did not conceive (3284 ± 2390 pg/ml versus 2809 ± 1225 pg/ml respectively).

Akagbosu et al. (1998) described a woman with severe male factor infertility having two ICSI cycles. Of 19 injected oocytes, on her first ICSI cycle in which OHSS developed, only one fertilized. On the following ICSI cycle, this time without OHSS, normal fertilization, cleavage, implantation and delivery were observed (Akagbosu et al., 1998). It was hypothesized that OHSS may have a possible detrimental effect on the quality of the oocytes. If so, it may have detrimental effects on the quality of the embryos and the developing pregnancy at its early stages and thus may cause

Table I. The characteristics and COH outcome of the OHSS patients—comparison between conception and non-conception cycles

<table>
<thead>
<tr>
<th></th>
<th>Delivered</th>
<th>Non-pregnant</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>28 ± 4.5</td>
<td>29.4 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean infertility</td>
<td>4 ± 2.9</td>
<td>3.9 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>duration (years)</td>
<td>8.4 ± 6.9</td>
<td>6.2 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>33.7 ± 12.6</td>
<td>32.2 ± 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>HMG amp</td>
<td>12 ± 2.4</td>
<td>12 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>HMG days</td>
<td>2390 pg/ml</td>
<td>2809 ± 1225</td>
<td>NS</td>
</tr>
<tr>
<td>E2 on HCG day (pg/ml)</td>
<td>2078 ± 1223</td>
<td>306 ± 583</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Follicles</td>
<td>21.4 ± 9</td>
<td>20.8 ± 9.4</td>
<td>NS</td>
</tr>
<tr>
<td>Oocytes</td>
<td>20 ± 9</td>
<td>19.5 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Embryos</td>
<td>9 ± 5.7</td>
<td>6.8 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mid-luteal E2 (pg/ml)</td>
<td>1472 ± 1239</td>
<td>1216 ± 975</td>
<td>NS</td>
</tr>
<tr>
<td>E2 14 days after</td>
<td>0.9 ± 2.9</td>
<td>12 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital duration (days)</td>
<td>7.6 ± 6.6</td>
<td>5.2 ± 3.2</td>
<td>P &lt; 0.02</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*Student’s t-test.
NS = not significant; E2 = estradiol.

Table II. The characteristics and COH outcome in OHSS patients who conceived—comparison between patients who delivered and those who aborted

<table>
<thead>
<tr>
<th></th>
<th>Delivered</th>
<th>Aborted</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>28.5 ± 4.9</td>
<td>27.3 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean infertility</td>
<td>4.2 ± 3.3</td>
<td>3.6 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>duration (years)</td>
<td>5.9 ± 2.9</td>
<td>6.2 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>7.2 ± 7</td>
<td>10.4 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>34.5 ± 12.3</td>
<td>32.4 ± 13.2</td>
<td>NS</td>
</tr>
<tr>
<td>HMG ampules</td>
<td>12 ± 2.3</td>
<td>12.4 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>E2 HCG day (pg/ml)</td>
<td>3165 ± 2385</td>
<td>3471 ± 2440</td>
<td>NS</td>
</tr>
<tr>
<td>Follicles</td>
<td>20.5 ± 8.7</td>
<td>23 ± 9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Oocytes</td>
<td>18.5 ± 8.4</td>
<td>21.9 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Embryos</td>
<td>8.4 ± 4.5</td>
<td>10 ± 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Embryo/transfer</td>
<td>3.3 ± 0.9</td>
<td>2.9 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mid-luteal E2 (pg/ml)</td>
<td>1481 ± 1335</td>
<td>1462 ± 1125</td>
<td>NS</td>
</tr>
<tr>
<td>Mid-luteal P4 (ng/ml)</td>
<td>57 ± 18</td>
<td>47 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>E2 14 days after</td>
<td>2133 ± 1128</td>
<td>1979 ± 1404</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital duration (days)</td>
<td>5.9 ± 3.2</td>
<td>10.5 ± 9.6</td>
<td>P &lt; 0.02</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*Student’s t-test.
E2 = estradiol; P4 = progesterone
pregnancy loss. Further study is warranted before drawing firm conclusions regarding this hypothesis.

Dulitzky et al. (1999) found positive markers of thrombophilia in 13 of 15 (86.6%) of women hospitalized for severe OHSS compared with eight of 41 control women (19.5%, \( P < 0.01 \)). They hypothesized that high prevalence of positive thrombophilic markers may shed new light on the pathophysiologic mechanism of OHSS (Dulitzky et al., 1999). Thrombophilia have been related to recurrent miscarriages in women (Dulitzky et al., 1999). High prevalence of thrombophilic markers in severe OHSS may be the explanation for the increased rate of pregnancy loss that was found in our patients.

Although the follicular and luteal phase hormonal profiles were similar in the patients who delivered and the ones who aborted, the patients who miscarried had a more severe form of OHSS, as reflected by a longer stay in hospital (an average stay of 6 days compared with 11 days respectively). The haemoconcentration, electrolyte imbalance, hypoxia, liver and renal dysfunction that are present in severe and critical OHSS may cause haemodynamic instability that is probably not harmful to the implantation process but may affect early pregnancy subsequent to implantation.

The association of PCOS and OHSS has been considered in previous studies. Persistantly high concentrations of LH have been associated with increased rates of miscarriages (Homburg, 1998) and it is well accepted that PCOS patients are prone to developing OHSS (Karabacak et al., 1998). However, since none of our patients with OHSS had typical PCOS, high serum LH levels were not the reason for the increased rate of miscarriage that was found.

In conclusion, the clinical pregnancy rate of IVF patients who developed severe OHSS was significantly higher than that in patients without the syndrome. Nevertheless, their abortion rate was also significantly higher. Patients with OHSS who conceived had a more severe clinical course necessitating a longer stay in hospital. OHSS, necessitating hospitalization, is a detrimental clinical situation not only for the mother but also for the developing pregnancy. This would certainly have an impact on patient counselling, patient care and use of COH protocols in ART.

References


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