Early and late ovarian hyperstimulation syndrome: early pregnancy outcome and profile

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BACKGROUND: Ovarian hyperstimulation syndrome (OHSS) in IVF/ICSI cycles may occur either as an early (early onset) or a late pattern (late onset). This observational study was designed to identify whether the onset pattern of OHSS is associated with the occurrence of pregnancy and the early pregnancy outcome. METHODS: Among 4376 consecutive IVF/ICSI cycles, 113 patients were hospitalized for OHSS after IVF/ICSI treatment and were included in the study. The setting was the Dutch-speaking Brussels Free University Hospital, between June 2000 and September 2002. RESULTS: Early OHSS occurred in 53 patients, and late OHSS complicated 60 patients. A total of 96.7% of the late OHSS cases occurred in a pregnancy cycle and were more likely to be severe than the early cases \( (P < 0.05) \). Although in the early group there initially was a 41.5% positive HCG rate per cycle, the clinical pregnancy rate fell to 28.3% as a result of a significantly \( (P < 0.05) \) increased preclinical pregnancy loss rate compared with the non-OHSS patients (31.8 versus 88.3%, respectively). The ongoing pregnancy rate per cycle was 14.4% in the early and 26.4% in the late group. Multiple pregnancy rates were high in both groups (40 and 45.5%, respectively), but only in the late group did the incidence reach significance compared with the non-OHSS population (45.5 versus 29.1%, \( P = 0.02 \)). Estradiol levels and number of follicles on the day of HCG were significantly higher in the early OHSS group. However, there was no difference in estradiol values on the day of hospital admittance between the two groups. In addition, the number of follicles on the day of HCG administration appears to be a better prognostic indicator for the occurrence of severe OHSS than the estradiol values (87% of the severe cases had \( \geq 14 \) or follicles of a diameter \( \geq 11 \) mm, whereas only 50% of them had an estradiol value \( \geq 3000 \) ng/l). CONCLUSIONS: The early OHSS pattern is associated with exogenously administered HCG and a higher risk of preclinical miscarriage, whereas late OHSS may be closely associated with the conception cycles, especially multiple pregnancies, and is more likely to be severe. Further clarification of these two different clinical entities could have implications for research protocols as well as for preventive and management strategies for OHSS.

Key words: complications/early/late/OHSS/pregnancy outcome

Introduction

Stimulation and induction of multifollicular growth by gonadotrophins remains the first step in any standard stimulation protocol used for assisted reproductive technology (ART). However, the use of these drugs is not without side effects. Ovarian hyperstimulation syndrome (OHSS) is the most common complication. Although significant OHSS has a relatively low incidence (~2%), it may in severe cases result in a potentially life-threatening situation (Mathur et al., 2002). The pathogenesis of OHSS is a complex process that may result from the interaction of endocrine and paracrine factors (cytokines) (Mathur and Jenkins, 2001). However, the increased capillary permeability with the resulting loss of fluid into the third space are the main pathophysiological events. HCG seems to be the pivotal stimulus of the syndrome in a susceptible woman (Al-Shawaf and Grudzinskas, 2003; McElhinney et al., 2002).

Lyons et al. (1994) were the first to describe two distinct patterns of OHSS: the early type that occurred 3–7 days after ovulation triggering by HCG, and the late type that occurred 12–17 days after HCG. Early OHSS is an acute consequence of the exogenous HCG administration before oocyte retrieval and is usually related to an excessive ovarian response to gonadotrophin stimulation (Navot et al., 1992; Mathur et al., 2002). Late OHSS is induced by endogenous HCG from the initiated pregnancy and is observed only in patients who become pregnant, especially in those with more than one initial gestational sac (Navot et al., 1992).
The initial FSH dose was fixed for the first 5 days of treatment. Follicle mone levels were within the appropriate values already mentioned. Ovarian stimulation was achieved by the use of a GnRH agonist (nasal buserelin (Suprefact, Aventis Pharma, Germany) 600 μg daily, or Cetrorelix, Serono SA) administered s.c., or HMG (Menopur, Serono, Switzerland) or HMG (Menopur, Serono SA) administered s.c.; when the criterion of the presence of at least three follicles of 18 mm was met.

However, there are issues yet to be defined. The number of OHSS cases that have been included in the studies is relatively small (11 and 78, respectively) and some conclusions are controversial (late OHSS cases occurred only in multiple gestations in the first report; and the number of oocytes retrieved was higher in cycles where late OHSS occurred than in cycles without OHSS, in the second report). Furthermore, controversy still exists in the literature with regards to the predictive value of the estradiol levels and number of follicles on the day of HCG administration in identifying a patient who is at high risk during ovarian stimulation treatment for IVF (Aboulghar, 2003; Orvieto, 2003; Delvigne et al., 1993; Blankstein et al., 1987). This might be due to the fact that there is no distinction according to the type of OHSS.

The aim of this observational study is to report on a large number of OHSS cases in a single centre, with respect to presentation pattern and its association with pregnancy incidence and early pregnancy outcome.

**Materials and methods**

Between July 2000 and September 2002, a total of 4376 cycles of IVF/ICSI carried out with a GnRH analogue ovarian stimulation protocol reached the oocyte retrieval stage (oocyte pick-up; OPU). This observational study included 113 patients, aged 22–41 years, who were hospitalized consecutively for OHSS. The study design was approved by the Ethical committee of the Vrije Universiteit Brussel, AZ-VUB, Brussels, Belgium. Patients hospitalized with OHSS after ovulation induction or after oocyte donation were not included in the study. The indications for fertility treatment were: female; male; combined; unexplained infertility; and preimplantation genetic diagnosis (PGD).

**Stimulation protocol**

Ovarian stimulation was achieved by the use of a GnRH agonist (n = 3087) or GnRH antagonist (n = 1289) protocol. According to the long GnRH agonist suppression protocol, patients received intranasal buserelin (Suprefact, Aventis Pharma, Germany) 600 μg daily for 21 days to suppress endogenous gonadotrophin secretion starting on day 21 of the cycle. Once the estradiol level was <80 ng/l and progesterone <1.5 μg/l, and in the absence of a dominant follicle, either recombinant human FSH (Puregon; NV Organon, Oss, The Netherlands, or Gonal-F; Serono, Switzerland) or HMG (Menopur, Ferring, Germany) injections commenced. The initial gonadotrophin dose remained fixed for 5–6 days. According to the short protocol, the agonist administration was initiated on day 2 of the cycle followed by gonadotrophin injections on day 3 (the same medications as mentioned above were used). In accordance with the GnRH antagonist protocol, on day 2 or 3 of the cycle, recombinant FSH injections were initiated (Puregon or Gonal-F) provided that the hormone levels were within the appropriate values already mentioned. The initial FSH dose was fixed for the first 5 days of treatment. Thereafter, based on the follicular growth and estradiol levels, the initial gonadotrophin dose could be adjusted until the final day of HCG administration. On day 6 of the stimulation, s.c. administration of the antagonist was started (Orgalutran, Organon 0.25 mg in 0.5 ml daily; or Cetroside, Serono SA, Geneva, Switzerland) up to and including the day of ovulation triggering by HCG.

In all the protocols, monitoring of both follicular growth (by transvaginal ultrasound) and hormone levels (estradiol, FSH, LH and progesterone) was performed, starting on day 6 of the stimulation and repeated as appropriate. The ovulation triggering dose of HCG was 10 000 IU (Pregnyl, NV Organon; or Profasi, Laboratories Serono SA) administered s.c., when the criterion of the presence of at least three follicles of 18 mm was met.

The luteal phase of the treatment cycles was supported by vaginally administered progesterone (Utrogestan; Besins International, Belgium) at a dosage of 600 mg daily in three equal doses beginning the day after ovulation triggering. In some cycles, a second dose of HCG (5000 IU) was administered 7 days after the first ovulatory dose.

Oocytes were inseminated within 4 h of retrieval either by classic IVF (34%) or by ICSI (66%). Embryo transfer was performed on day 3 (cleavage stage embryos) or on day 5 (blastocyst stage). The mean number of embryos transferred was two. To assess treatment outcome, serum β-HCG was measured 14 days after OPU and repeated 3 days later. A rise in serum HCG on two consecutive blood tests indicated pregnancy. A clinical pregnancy was defined as the ultrasound observation of fetal cardiac activity after 7 weeks of gestation. Pregnancy losses before this period were assigned as preclinical miscarriages (biochemical, blighted ovum, missed abortions and spontaneous abortions). An ongoing pregnancy was defined as a pregnancy with a positive heartbeat at ultrasound after 12 weeks of gestation.

**OHSS classification**

The severity of OHSS was graded according to the criteria of Navot et al. (1992). Moderate OHSS in particular is characterized by abdominal distension and discomfort, nausea ± vomiting ± diarrhoea, enlarged ovaries 5–12 cm and ultrasonographic evidence of ascites. Severe OHSS is characterized by variable ovarian enlargement; massive ascites ± hydrothorax; breathing difficulties; haematocrit >45%; white blood cell count >15 000; oliguria; creatinine 1.0–1.5; creatinine clearance ≤50 ml/min; liver dysfunction; and anasarca oedema.

Hospital admission was considered in all cases of moderate or severe OHSS. After confirmation of the diagnosis of OHSS, the patients were hospitalized and treated conservatively until the spontaneous resolution of the syndrome and the improvement of clinical and laboratory findings. In-patient management options were followed as suggested in the current literature (Aboulghar and Mansour, 2003; Delvigne and Rozenberg, 2003). In particular, fluid intake was restricted to 1500 ml per 24 h, to avoid fluid overload. Prophylactic anticoagulation was started with low molecular weight heparin (LMWH) in every patient until discharge. Drainage of abdominal ascites was performed when the patient was significantly symptomatic, i.e. dyspnoeic or with pathological abdominal discomfort. Human albumin, 200 ml (albumin 20%), was supplemented per litre of ascites drained, and for every 0.2 g/dl below a serum albumin level of 3.2 g/dl, as measured daily. Drainage of pleuritic fluid was performed only when indicated. According to clinical symptomatology and condition of the patient, medications were administered for symptomatic relief.

Classification of OHSS as early or late was performed according to the day of oocyte retrieval (Mathur et al., 2000). Therefore,
OHSS occurrence within 9 days after OPU was considered to be early OHSS and occurrence after 10 days was classified as late OHSS.

Data analysis
In total, 113 consecutive patients/cycles were analysed. The 1401 pregnancies that occurred in 4263 non-OHSS cycles served as a control group for the pregnancy outcome. Statistical analysis was performed using SPSS version 11.5 software. $\chi^2$ test was used to analyse nominal variables in the form of frequency tables. Normally distributed (Kolmogorov–Smirnov test with Lilliefors correction) metric variables were tested with the t-test for independent samples, while non-normally distributed metric variables were analysed with the Mann–Whitney U-test. All tests were two-tailed with a confidence level of 95% ($P < 0.05$). Values are expressed as the mean ± SEM.

Results
General outcome
A total of 113 consecutive OHSS cases were identified in the study period and finally analysed. ‘Early’ OHSS occurred in 53 patients, and ‘late’ OHSS affected 60 patients. The incidence of OHSS was 2.6% (113 out of 4376 IVF cycles).

There were no statistically significant differences between the two groups in terms of patient age and aetiology of infertility. The overall prevalence of polycystic ovaries was 14.7% (18.5% in the early group versus 11.5% in the late group, $P > 0.05$). There were no differences with regards to stimulation protocol, duration of stimulation and total dose of gonadotrophins between the two groups. In nine patients with early OHSS, the transfer of the embryo was cancelled due to the occurrence of ($n = 7$) or the fear of developing ($n = 2$) OHSS (Table I).

Late OHSS cases were significantly more likely to be severe than the early cases ($P < 0.05$). In addition there were significantly more hospitalization days with late OHSS (7.9 versus 4.6, $P < 0.05$). The mean time between the OPU and the moment of occurrence of OHSS was 4.7 days in the early and 13.7 days in the late type, respectively. However, two patients in the early group required re-hospitalization because of late OHSS (Table II).

Estradiol and the number of follicles were significantly higher in both types of OHSS compared with the non-OHSS patients (Table III). The number of follicles on the day of HCG administration was significantly higher in the early group than in the late group (22.5 versus 17.7, $P < 0.001$). Similarly, a significant difference was observed in the number of oocytes retrieved (22.1 versus 15.3, $P < 0.001$). Although peak estradiol concentrations measured on the day of HCG were significantly higher in the early than in the late group, they were not significantly higher on the day of hospital admission (3158 versus 2861, $P > 0.05$). If a threshold of 3000 ng/l had been used, only 50% of all severe cases would have been identified as high-risk patients. Similarly, only 46.2% of the early OHSS patients would have been classified as at high risk of developing OHSS. In contrast, if a threshold of 14 follicles (diameter ≥11 mm) had been used, 98.1% of the early cases and 86.8% of the total severe cases would have been predicted (Table III).

Pregnancy outcome
Almost all the late OHSS cases occurred in a pregnancy cycle (96.7%). There were two patients who presented late OHSS without being pregnant. Both of them had received a second dose of HCG on day 7 and day 8, post-OPU, respectively. Examining their daily monitoring flow charts (data not shown), it was found that a declining pattern for estradiol and progesterone was present until the second HCG dose. Four days later, they presented moderate OHSS and were hospitalized for 2 and 4 days, respectively.

The clinical pregnancy rates and the ongoing pregnancy rate in the late group were 91.8 and 88.3%, respectively. In the early group, although we obtained a biochemical pregnancy rate of 41.5% per cycle, the clinical pregnancy rate was reduced to 28.3% per cycle due to an increased preclinical pregnancy loss rate (31.8% compared with 14.4% in the non-OHSS group, $P < 0.05$). There was no difference between the two groups with regards to the incidence of clinical miscarriages (5.8% in the early and 5.3% in the late OHSS group). The multiple pregnancy rates did not differ significantly between the two OHSS types (40 and 45.5%, respectively) but, comparing the late group with the non-OHSS patients, there was a statistically significantly higher incidence of multiple pregnancies (45.5 versus 29.1%, respectively) (Table IV).

All the patients received progesterone as luteal support. However, 21 patients (39%) in the early group and 15 patients (25%) in the late group had received an additional second dose of HCG as luteal supplementation. In

Table I. Patient characteristics and stimulation protocol parameters

<table>
<thead>
<tr>
<th></th>
<th>Early ($n = 53$)</th>
<th>Late ($n = 60$)</th>
<th>Total patient cycles ($n = 113$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SEM)</td>
<td>30.7 ± 0.6</td>
<td>31.4 ± 0.5</td>
<td>30.9 ± 0.4</td>
</tr>
<tr>
<td>Indication for IVF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (17.0%)</td>
<td>14 (23.3%)</td>
<td>23 (20.3%)</td>
</tr>
<tr>
<td>Tubal</td>
<td>3 (5.6%)</td>
<td>6 (10.0%)</td>
<td>9 (8.4%)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>2 (3.7%)</td>
<td>4 (6.6%)</td>
<td>6 (7.6%)</td>
</tr>
<tr>
<td>PCO</td>
<td>4 (7.4%)</td>
<td>3 (5.0%)</td>
<td>7 (5.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (1.7%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (52.8%)</td>
<td>27 (45.0%)</td>
<td>55 (48.6%)</td>
</tr>
<tr>
<td>Combined</td>
<td>10 (18.9%)</td>
<td>8 (13.3%)</td>
<td>18 (15.9%)</td>
</tr>
<tr>
<td>PCO</td>
<td>6 (11.3%)</td>
<td>4 (6.5%)</td>
<td>10 (8.8%)</td>
</tr>
<tr>
<td>PGD</td>
<td>4 (7.5%)</td>
<td>3 (5.0%)</td>
<td>7 (6.2%)</td>
</tr>
<tr>
<td>Unexplained</td>
<td>2 (3.7%)</td>
<td>8 (13.3%)</td>
<td>10 (8.8%)</td>
</tr>
<tr>
<td>Stimulation protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonist</td>
<td>21 (39.6%)</td>
<td>32 (53.3%)</td>
<td>53 (46.9%)</td>
</tr>
<tr>
<td>Antagonist</td>
<td>32 (60.4%)</td>
<td>28 (46.7%)</td>
<td>60 (53.1%)</td>
</tr>
<tr>
<td>Duration of stimulation (days ± SEM)</td>
<td>11.2 ± 0.2</td>
<td>10.8 ± 0.2</td>
<td>10.9 ± 0.1</td>
</tr>
<tr>
<td>Total dose of gonadotrophins (IU ± SEM)</td>
<td>2404 ± 102</td>
<td>2147 ± 104</td>
<td>2250 ± 71</td>
</tr>
<tr>
<td>Cancelled cycles</td>
<td>9</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

PCO = polycystic ovaries; PGD = preimplantation genetic diagnosis; NA = not applicable; NS = not statistically significant; SS = statistical significance ($P < 0.05$).
the subgroup with early onset OHSS plus HCG for luteal support, all patients were admitted to hospital within 3 days after HCG supplementation. The mean duration of hospitalization was 4.2 days, and only two patients in this group developed severe OHSS. None of the early onset OHSS-positive HCG tests was related to the luteal support dose of HCG as all the first pregnancy tests were carried out on the 14th day after the OPU date.

A multivariate logistic regression analysis failed to find any covariate with a statistically significant effect on
pregnancy occurrence and outcome in the two study groups (data not shown).

Discussion

Our results confirm previous conclusions by other authors (Lyons et al., 1994; Mathur et al., 2000) that OHSS occurs as two distinct clinical entities depending on the timing of onset. Late OHSS nearly always occurs in relation to pregnancy (Table IV). This is the first time that late OHSS is reported as being able to complicate a non-conception cycle. The two patients who developed ‘late’ OHSS without being pregnant had been treated with additional administration of HCG during the luteal phase. In addition, 21 patients who received a second dose of HCG for luteal support were admitted to hospital within 3 days after the HCG supplementation with early-onset OHSS, which suggests a higher incidence of OHSS in patients who received HCG as luteal support (Belaisch-Allart et al., 1990).

Although late OHSS is strongly associated with pregnancy, a surprisingly high initial pregnancy rate was observed even in early OHSS (50% per embryo transfer). Nevertheless, we found a statistically significant increased preclinical miscarriage rate (31.8%) in the early group, compared with non-OHSS patients (14.4%) and the late OHSS group (5%). On the other hand, we observed a low clinical miscarriage rate of 4.3% in all OHSS patients which is comparable with 10.5% in the non-OHSS population (P > 0.05). Our findings suggest that once a clinical pregnancy has been established in a patient with OHSS (both early and late OHSS), there is a normal risk of abortion. On the contrary, when an embryo has implanted in a profoundly altered endocrine and paracrine environment, as is the case with early OHSS (Table III), it carries a high risk of preclinical miscarriage. This is a novel finding and it might be associated with altered endometrium receptivity in stimulation cycles (Bourgain and Devroye, 2003). It has been demonstrated that high serum estradiol concentrations on the day of HCG injection are detrimental to uterine receptivity without affecting embryo quality (Simon et al., 1995). Moreover, we have reported previously that endometrial advancement is present on the day of the oocyte retrieval, in both gonadotrophin/agonist and antagonist stimulation cycles, and an excess prevents the occurrence of pregnancy (Ubaldi et al., 1997; Kolibianakis et al., 2002).

There are two studies examining the pregnancy outcome in OHSS patients (Abramov et al., 1998; Mathur and Jenkins, 2000). The largest study in the literature (Abramov et al., 1998) suggests an association between miscarriage and OHSS, given a total clinical miscarriage rate of 29.8% of which 25% were early (7–13 weeks) and 4.8% were late miscarriages (13–20 weeks). However, only severe cases of OHSS were investigated, and preclinical pregnancies were not included as an outcome measure, which precluded a comparison of results; in addition, contemporaneous pregnancies from the same country (Israel) without OHSS were not used as a control group, but historical controls from several countries were used instead. The British study (Mathur and Jenkins, 2000), although smaller in sample size and not including data on preclinical pregnancies, did use a contemporaneous control group. In accordance with our results, the number of miscarriages was found not to be significantly different between the two groups: total clinical (7–20 weeks of gestation) miscarriage rate 12.2 versus 16.8% among OHSS pregnancies and the control pregnancies, respectively. This discrepancy in terms of clinical miscarriage rate compared with the Israeli study might be explained because only severe and critical cases were investigated by Abramov and co-authors, whereas our study as well as the British study included both moderate and severe cases. Therefore, the higher metabolic derangement during severe OHSS might potentially have a greater effect on a developing pregnancy.

In accordance with previous reports (Mathur et al., 2000), we found a statistically significantly higher incidence of multiple pregnancies within the late OHSS compared with the non-OHSS patients (45.5 versus 29.1%, respectively). Although Mathur et al. (2000) reported that the rates of multiple pregnancy associated with late OHSS are significantly higher than those in the early group, the present study showed a 5.5% difference in favour of the late type, although this was not statistically significant (45.5 versus 40%, respectively). This increased incidence of multiple pregnancies in patients with OHSS indicates the impact of endogenous HCG in the pathogenesis of OHSS. Particularly in late OHSS, we might even consider it another complication of the high order pregnancies associated with ART.

Late OHSS cases were more likely to be severe and they account for 68% of the total severe cases of OHSS. The number of follicles, although more sharply increased in early OHSS, was significantly higher compared with non-OHSS patients in both types of the disease. Furthermore, it appears that the number of follicles with a diameter in excess of 11 mm has higher sensitivity, compared with estradiol, for predicting the disease, especially with regards to early or severe cases (Table III). Although early and late OHSS are different clinical entities, this does not mean that they have a different pathophysiology. If the aetiology is a specific mutation which renders some patients susceptible to OHSS, as has been described recently (Kaiser, 2003; Montanelli et al., 2004), the common denominator of the disease is the multifollicular growth and the quantity of the vasoactive factor produced by HCG-triggered/granulosa cells. The released vasoactive factor, above a certain threshold, induces significant vascular hyperpermeability. This threshold, in the case of the early pattern, is reached at an earlier stage because of the higher number of follicles compared with late OHSS and the bolus injection of HCG. In the late type, this occurs later as it depends on the gradually increasing HCG produced by the implanting trophoblast, which again stimulates a higher number of follicles compared with non-OHSS patients. Especially in multiple pregnancies, the higher levels of HCG induce the secretion of higher amounts of vasoactive factors, thus contributing to a higher risk for development of the disease. The sustained action of rising HCG might also explain the higher severity of late OHSS. The only issue that still
needs to be addressed is why not all of the early OHSS women have further exacerbation of their OHSS when they become pregnant, and HCG is on the increase again. One explanation might be that the biochemical compartment of the cell, which produces the pathogenetic vasoactive factor under the action of HCG, has a capacity that is different from the compartment that produces progesterone or estradiol and therefore there is a gradual decrease of the vasoactive response. Another explanation could be different susceptibility phenotypes for the two forms of the condition.

In conclusion, this study confirms the occurrence of OHSS both in an early-onset pattern related to exogenously administered HCG, and in a late pattern under endogenous stimulation due to secreted HCG from an implanting pregnancy. Moreover, early occurrence of the disease is associated with a high preclinical miscarriage rate. Although they occur as different clinical entities, they share a common background of excess ovarian follicle growth. As Orvieto (2003) has already stated, elevated estradiol rather is an incidental factor. Future preventative strategies should rely on reduced follicular stimulation; replacing the HCG ovulation triggering dose with other medications; and the further reduction of multiple pregnancy rates by implementing single embryo transfers.

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References

Aboulghar MA (2003) Prediction of ovarian hyperstimulation syndrome. Estradiol level has an important role in the prediction of OHSS. Hum Reprod 18,1140–1141.


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