Symposium: Update on prediction and management of OHSS

Outcome of IVF pregnancies following severe OHSS

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Abstract

Because severe ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening iatrogenic complication, much effort is made to prevent it and the anticipated pregnancy naturally becomes of secondary importance. There are many publications on OHSS, but very few on pregnancy outcomes. This work is to review the effect of OHSS on pregnancy outcome along the pregnancy course. Hospitalized patients with severe OHSS are exposed to several insults that could affect pregnancy outcome in its early stages: the ovarian hyperstimulation for IVF itself, haemodynamic instability that involve haemoconcentration, hypoxia, liver and renal dysfunction, and exposure to high endogenous oestrogens, cytokines, renin, angiotensin and prostaglandins. There is a paucity of data on the relation of OHSS and pregnancy complications. The incidence of multiple pregnancies, gestational diabetes mellitus, placental abruption prematurity and low birthweight is higher in cases of pregnancy complicated by severe OHSS. Therefore, these pregnancies should be considered as high-risk pregnancies, and followed/treated as such. As prevention is the best 'treatment' for OHSS, this may imply the need for more patient-friendly or mild stimulation protocols.

Keywords: *IVF, ovarian hyperstimulation syndrome, pregnancy complications, pregnancy loss, pregnancy outcome*

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a familiar and yet unwanted phenomenon to clinicians in fertility therapy. Severe OHSS is characterized by increased vascular permeability and, thus, the shift of fluids from blood vessels to extravascular space. As such, the condition often requires hospitalization and in its critical form may require admission to an intensive care unit (Whelan III and Viahost, 2000).

Because 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 becomes of secondary importance. This review aims to concentrate on the impact of OHSS on pregnancy outcome along the pregnancy course: from the early stages after conception until the end of pregnancy and delivery.

A review of published studies

In order to assess the outcome of IVF pregnancies complicated by severe and critical OHSS, Abramov *et al*. (1998) reviewed the medical records of all patients hospitalized between January 1987 and December 1996, in a multicentre study of 16 tertiary hospitals, in Israel. Severe and critical cases were selected according to the criteria reported by Golan *et al*. (1989). Standard definitions were used to evaluate pregnancy outcome parameters: only clinical pregnancies were included, early miscarriage occurred before week 13 of gestation and late miscarriage up to week 20 of gestation. Pregnancy-induced hypertension (PIH) was defined as hypertensive disorder of pregnancy beyond 20 weeks of gestation with values of >140/90 twice or an increase of 30 mm Hg systolic or 15 mm Hg diastolic pressure with proteinuria. Gestational diabetes was diagnosed when two abnormal values were detected in 3 h oral glucose tolerance test. Major congenital malformation was considered if surgical intervention was required, a major organ was involved or it caused functional problems.

Of 2902 hospitalized patients for OHSS, 209 were in the severe or worse state, and 163 were IVF patients. Most were young (29 ± 4.5 years), healthy, with a mean of 4.4 ± 0.8 years infertility duration, of them 62% suffered from primary infertility. Anovulation was the common cause for infertility (36%), followed by male (23%) and mechanical (13%) factor. The clinical pregnancy rate was 73.2%: 42% singletons, 34% twins, 17% triplets and 7% quadruplets. Miscarriage rate was 29.8% of which 25% were early and 4.8% were late abortions. Of the three terminations of pregnancy, one was performed for deteriorating respiratory distress syndrome and two for fetal anomalies. Spontaneous fetal reduction (vanishing twin) occurred in 18%, whereas induced reduction was performed in 25% of the multiple pregnancies with 13% reduction-related abortion rate. Threatened abortion occurred in 18% of patients and hyperemesis gravidarum in 3% of them. Perinatal complications in the hospitalized patients for OHSS were compared with perinatal complications of all IVF patients at similar timing and place, as published by Friedler *et al.* (1992). Premature rupture of membranes was found in 18% of patients (compared with 5% in general IVF population), PIH in 13% (compared with 6%), gestational diabetes mellitus (GDM) in 6% (compared with 0.8%) and placental abruption in 4.4% (compared with 0.4%). One case of pulmonary embolism and one of intrauterine fetal death were also reported. Regarding deliveries, 29 of 68 were singleton, 34 were twins and the remaining five were triplets. The mean gestational age was 37 ± 3.2 weeks for singletons, 35 ± 2.2 weeks for twins and 34 ± 2.8 weeks for triplets. Four per cent of all deliveries occurred before term: preterm deliveries were in 28% of the singleton pregnancies, 50% of the twins and 100% of the triplets. Birthweight <1000 g was found in 6% of all newborns. The rate of Caesarean section was 44% (24% among singletons, 53% among the twins and 100% in the triplets). Ten percent of the deliveries were instrumental. Spina bifida and truncus arteriosus were prenatally diagnosed in two fetuses and no other major malformations in the live newborns.

The authors explained that hospitalized patients with severe OHSS were exposed to several insults that could effect pregnancy outcome in its early stages: (i) ovarian hyperstimulation for IVF itself; (ii) haemodynamic instability that involved haemoconcentration, hypoxia, liver and renal dysfunction; and (iii) the exposure to high endogenous oestrogens (Schenker and Weinstein, 1978), cytokines (Abramov *et al.*, 1996, 1997), renin, angiotensin (Bergh and Navot, 1992) and prostaglandins (Bergh and Navot, 1992).

A higher pregnancy rate among IVF patients in whom OHSS developed compared to IVF patients without OHSS had already been reported (Golan *et al.*, 1988; Delvigne *et al.*, 1993) but not with such a large difference (73% versus 14%). So the severity of OHSS is related to the probability of conception and probably with a higher rate of multiple pregnancies. The miscarriage rate (30%) was higher than the rates of other patients who underwent IVF (around 20%). This was attributed by them to the haemodynamic instability and not to the developing fetus since no newborn with fetal anomalies was found among the patients.

Abramov *et al.* (1998) concluded that pregnancy rates, multiple gestation rate, miscarriage, gestational diabetes, placental abruption, prematurity and low birthweight were significantly higher among IVF patients with OHSS compared with the 'regular' IVF population. In light of the above, they offered closer antenatal observation to minimize obstetrical complications, more selective fetal reduction, and close surveillance of blood pressure and possible early use of low dose aspirin.

A commentary by Mathur and Jenkins (2000) asked the question: 'Is OHSS associated with a poor obstetric outcome?' They quoted their experience coming from the University of Bristol IVF service, between 1 January 1995 and 30 September 1998. During this period, 41 IVF clinical pregnancies complicated by moderate or severe OHSS were reported. Miscarriage rates did not differ between this group and a group of 501 contemporaneous clinical pregnancies resulting from IVF patients in whom OHSS did not occur. They criticized the data of Abramov *et al.* (1998) who showed a higher miscarriage rate in OHSS patients, saying that the study group was not compared with contemporaneous pregnant patients without OHSS. The absolute risk of miscarriage in their IVF patients was higher compared with that described in IVF studies from various other countries at that time. Mathur *et al.* (2000) presumed that the difference between their results and Abramov's data could be attributed to a higher incidence of multiple pregnancies and/or the possible greater severity of OHSS in the latter study. They concluded that, if studies show that OHSS adversely affects the outcome of IVF pregnancies, there will have be further consequences for obstetrical care and also a significant impact on prevailing protocols for ovarian stimulation before oocyte retrieval: a more gentle or patient-friendly regimen will be chosen and a shift away from maximum ovarian stimulation will be made. Their basic question concerning OHSS and pregnancy outcome has remained unanswered due to lack of sufficient data.

Raziel *et al.* (2002) analysed the pregnancy rate and outcome (abortions and deliveries) in 104 IVF patients hospitalized for severe and critical OHSS in a single institution during a 6-year period (January 1994 to December 2000). They compared the characteristics of pregnant and non-pregnant patients with severe OHSS, and those with ongoing pregnancies with those who aborted. The first observation of the authors was a prominent and consistent decline in the incidence of severe and critical OHSS cases after IVF, from 6.4% to 1.5% over the last 3 years of the study period. Pregnancy was achieved in 60 (58%) of the 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%) were late abortions. The pregnancy and abortion rates of the patients with severe OHSS were significantly higher than those of IVF patients without OHSS during the same period of time (1138/4922, 23% and 169/1138, 15%, 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%, $P < 0.004$).

Severe early-onset OHSS was diagnosed in 100 patients (defined as the onset of OHSS within 8 days of initial human chorionic gonadotrophin (HCG) exposure relating to excessive pre-ovulatory response to stimulation). Late-onset 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 the serum oestradiol concentration 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.

The parameters with significantly different characteristics among patients with IVF conception cycles with severe OHSS were mean age, mean number of HMG ampoules utilized during the ovarian stimulation and treatment duration 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 oestradiol values on the day of HCG administration were similar in those who delivered and those who aborted (3165 ± 2385pg/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, $P < 0.01$).

This review 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. Other studies have found miscarriage rates of 29.8% (Abramov *et al.*, 1998) 28.6% (MacDougall *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/gamete intra-Fallopian transfer 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).

High miscarriage rates, such as these – whether from one centre or many centres – should have an explanation. Several hypotheses have been suggested by a number of investigators to explain the high miscarriage rate after OHSS: excessively high endogenous oestradiol concentrations (Simon *et al.*, 1998); abnormal cytokine concentrations (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 oestradiol concentrations that may harm early pregnancy was not supported by the data: the oestradiol concentrations on the day of HCG administration were similar in those patients with severe OHSS who delivered and those who aborted (3165 ± 2385 pg/ml and 3471 ± 2440 pg/ml, respectively). A trend for higher oestradiol concentrations 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).

Dulitzky *et al.* (1999) found positive markers of thrombophilia in 13 of 15 (86.7%) of women hospitalized for severe OHSS compared with eight of 41 control women (19.5%, $P < 0.01$). They postulated that the high prevalence of positive thrombophilic markers may shed new light on the pathophysiology of OHSS. Thrombophilia has been related to recurrent miscarriages in a number of studies over recent years (see Raziel *et al.*, 2001). High prevalence of thrombophilic markers in severe OHSS may be the explanation for the increased rate of pregnancy loss that was found in the above patients.

The conclusion of Raziel *et al.* (2002) was that 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 ovarian stimulation protocols in assisted reproduction treatments.

Wiser *et al.* (2005) investigated the medical records of all pregnancies that progressed beyond the first trimester in all patients who were hospitalized for severe OHSS, between January 1992 and December 2001, at the Shiba Medical Center, Israel. They compared the results with patients who conceived after IVF but did not develop severe OHSS. They divided singletons and twin pregnancies and also reported on serious events that occurred.

The study group included 165 patients with OHSS (101 singletons and 64 twins) compared with 156 patients without OHSS (85 singletons and 71 twins). They did not find significant difference in the incidence of GDM and PIH between the groups: GDM presented with 9.9% for singleton and 9.4% for twins in the OHSS group compared with 12.9% and 7% in the control group. PIH presented with 6.9% for singleton and 10.9% for twins in the OHSS group and 8.2% and 7% in the control group.

The singleton pregnancies in the OHSS and control groups were similar concerning gestational age and mean birthweight. Caesarean section was the mode of delivery in 24% of the singletons in the study group, versus 21.1% in the control group. Twins were delivered at similar gestational ages (35.3 ± 3.4 weeks and 35.7 ± 3.2 weeks, respectively). The rates of GDM and hypertensive disorders in general were higher in the study group compared with the rates in the general population: GDM 2.5% and PIH 3.7% (Ventura *et al.*, 2000; Xiong *et al.* 2001). The authors explain the high rates of GDM and PIH by the 'mother predisposition' having polycystic ovaries or by patients with high concentrations of endothelin 1, a potent vasoconstrictor, in the follicular fluid of patients undergoing ovulation induction, suggesting that it has a role in early pregnancy vascular development with late hypertensive effects in the third trimester. (Kamada *et al.*, 1993).

Papanikolaou *et al.* (2005), from the Dutch-Speaking Brussels Free University, Belgium, raised an interesting aspect concerning the onset of OHSS (whether early- or late-onset OHSS), and pregnancy outcome. Their overall incidence of OHSS was 2.6% (113 out of 4376 IVF cycles). Early-onset OHSS occurred in 53 patients and late-onset OHSS in the remaining 60 patients. Polycystic ovary disease was diagnosed overall in 14.7% of the patients: 18.5% in the early-onset group versus 11.5% in the late-onset group, $P \leq 0.05$.

Other characteristics between the two groups were similar. Late-onset OHSS patients were more likely to be severe than the early-onset cases as reflected by longer hospitalization period (7.9 days versus 4.6 days, $P < 0.05$). The biochemical pregnancy rate in the early-onset OHSS group was 41.5% ending in only 28.3% clinical pregnancy rate per cycle due to an increased pregnancy loss rate. The clinical pregnancy rates and the ongoing pregnancy rate in the late-onset OHSS group were 91.8% and 88.3%, respectively. The incidence of miscarriages between early- and late-onset OHSS patients was similar (5.8% and 5.3%, respectively). The multiple pregnancy rates were high (40% and 45.5%, respectively) compared with 29.1% in the non-OHSS group.

They suggest that once a clinical pregnancy has been achieved in a patient with OHSS (either early- or late-onset), there is a normal risk of abortion. If pregnancy is established in an altered endocrine and paracrine hostile condition, as in the case of early-onset OHSS, it carries a high risk of preclinical miscarriage. The unanswered question is why did not all of the patients with early-onset OHSS develop exacerbation of their OHSS when they become pregnant and HCG concentrations are further increased.

Outcome of pregnancies following severe OHSS in IVF patients according to the published large series are summarized in **Table 1**.

Conclusions

Pregnancy rates of IVF patients with OHSS are higher compared with the pregnancy rates of non-OHSS patients; however, miscarriage rates are probably higher, especially in its severe and critical presentation. Severe OHSS has deleterious effects not only on the patient but also on the fetus. As to whether OHSS itself causes or has any adverse effect on the coming pregnancy is still unknown. There is not enough data on the relation of OHSS and pregnancy complications. The heterogeneity of those few studies that have been published is an obstacle in making appropriate comparisons and conclusions. Only comparison of singleton IVF pregnancies (OHSS free versus OHSS complicated) would allow appropriate conclusions, as the majority of late-onset OHSS cases are multiple pregnancies. It seems that the incidence of multiple pregnancies, GDM, placental abruption, prematurity and low birthweight is higher in cases of pregnancy complicated by severe OHSS. Therefore, such a pregnancy should be considered as a high-risk pregnancy, and followed/treated as such. As prevention is the best treatment for OHSS, this may imply the need for more patient-friendly or gentle stimulation protocols, including use of GnRH antagonists and GnRH triggering before oocyte retrieval. New emerging IVF techniques, free of the risk of OHSS, such as vitrification of oocytes or embryos and in-vitro maturation of oocytes are also promising.

Table 1. Outcome of pregnancies following IVF in patients with severe ovarian hyperstimulation syndrome.

Publication	*No of OHSS patients*	*Clinical pregnancy rate per transfer (%)*	*Clinical miscarriage rate (%)*	*Gestational age at birth (weeks, mean ± SD)*	*Caesarean section (%)*
Abramov *et al.*, 1998	163	41.7	Early-onset OHSS: 25 Late-onset OHSS: 4.8 Total: 29.8	All births: 37 ± 3.2 Singleton: 37 ± 3 Twins: 35 ± 2.8 Triplets: 34 ± 2.8	44
Mathur *et al.*, 2000	41	No data	12.2	No data	No data
Raziel *et al.*, 2002	104	58	Early-onset OHSS: 18.3 Late-onset OHSS: 3.8 Total: 22.1	No data	No data
Wiser *et al.*, 2005	145	No data	(Only pregnancies beyond first trimester included)	All births: 35.3 ± 3.2 Singleton: 35.3 ± 3.4 Twins: 35.7 ± 3.2	24
Papanikolaou *et al.*, 2005	113	Early-onset OHSS: 8.3 Late-onset OHSS: 91.8 Total: 62	Early-onset OHSS: 6.6 Late-onset OHSS: 3.6 Total: 4.3	No data	No data

Only large published series were included.

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