Course of Ovarian Hyperstimulation Syndrome in 19 Intact Twin Pregnancies After Assisted Reproduction Techniques, With a Case Report of Severe Thromboembolism

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Ovarian hyperstimulation syndrome (OHSS) is a serious complication of assisted reproduction techniques using in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI). Its etiology has still not yet been fully resolved. Human chorionic gonadotrophin, administered exogenously as well as produced endogenously during pregnancy, is responsible for the onset of OHSS, and high levels of estradiol appear to worsen the condition. In this case series, the course of mild to severe OHSS was evaluated in 19 intact twin pregnancies after IVF/ICSI. Another serious complication associated with OHSS is thromboembolic events. In these cases, the pregnancy can be protected through anticoagulation treatment, but there may be exceptions to this. This series includes a case of bilateral thrombosis of the internal and external jugular veins in the 7th gestational week in a twin pregnancy after OHSS and ICSI, with termination of the pregnancy in the 9th gestational week due to progressive thrombosis during anticoagulation therapy.

Forty per cent of children born after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) are twins (Pinborg, 2005; Pinborg et al., 2004). The general consensus, with few exceptions, is that IVF/ICSI twins have neonatal outcomes (in terms of perinatal mortality, birthweight, gestational age, and small-for-gestational-age status) similar to those in twins conceived spontaneously (Pinborg, 2005; Pinborg et al., 2004). IVF/ICSI twins also have long-term outcomes similar to those in spontaneously conceived twins, with similar rates of neurological sequelae. However, twins conceived through IVF/ICSI techniques have considerably higher risks than IVF/ICSI singletons with regard to other short-term and long-term outcome measures (Pinborg, 2005; Pinborg et al., 2004).

Selective termination of pregnancy in IVF/ICSI twin pregnancies is usually performed for fetal abnormalities. In many countries, selective feticide in higher order multiple pregnancies is used to reduce the number of fetuses in order to maximize the pregnancy outcome of at least one healthy child (Pinborg, 2005; Pinborg et al., 2004). Induced abortion of a twin pregnancy because of maternal complications is fortunately rare.

There are no studies concerning only twin pregnancies conceived through IVF/ICSI with ovarian hyperstimulation syndrome (OHSS). Undoubtedly, the severity of OHSS increases in multiple pregnancies. Thromboembolic phenomena represent the most serious complications following assisted reproduction techniques. Deep vein thrombosis (DVT) in the upper extremities and jugular veins is a comparatively frequent complication (up to 10%) after OHSS, but these thromboembolic events in OHSS — even during anticoagulation treatment — do not necessarily result in termination of the pregnancy.

This study presents data for 19 patients with viable twin pregnancies after IVF/ICSI who developed mild to severe OHSS. One of these was a pregnancy with late-onset OHSS after ICSI, complicated by DVT in the jugular vein in the 7th gestational week. Progression of the thrombosis, despite high levels of anticoagulant drug treatment, led to termination of pregnancy in the 9th gestational week.

Materials and Methods

A retrospective analysis was carried out with records of patients who presented in 2000 to 2005 with mild to severe ovarian hyperstimulation syndrome after receiving IVF/ICSI treatment. Data recorded included the patients' age, the duration of the hospital stay,

Received 13 June, 2006; accepted 14 July, 2006.

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type of OHSS (early, late; mild, moderate, severe), duration of stay in the intermediate care unit, complications (bleeding, thrombosis), family history of thromboembolism, symptoms of OHSS (abdominal pain, dyspnoea, oedema, ascites, nausea, elevated temperature), treatment strategies (dopamine, hydroxyethyl starch, mannitol, diuretics), and pregnancy outcome (mode of delivery, gestational week at delivery). Data for several serum parameters for OHSS on the day of admittance to the hospital were also compared with the data on the patient's day of discharge from hospital (blood group, hemoglobin, hematocrit, platelets, human chorionic gonadotrophin, estradiol, progesterone, sodium, potassium, total protein, albumin, chloride, glucose, creatinine, protein, albumin, C-reactive protein, partial thromboplastin time, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase). The data are presented as means plus or minus standard deviation; Student's *t* test was used to assess the significance of all of the serological parameters studied.

Results

Of 174 patients with OHSS, 19 (10.9%) had twin pregnancies. These patients were 29 to 37 years of age, and the duration of their hospital stays ranged from 4 to 33 days. Six patients (31.6%) had early-onset OHSS, whereas 13 (68.4%) presented with late-onset OHSS. The time from embryo transfer to hospital admission ranged from 2 to 26 days. Thirteen patients were admitted to the intermediate care unit for up to 15 days (Table 1).

All patients, except one with mild OHSS, were treated with low-molecular-weight heparin (LMWH) and intravenous diuretics. Only one patient received mannitol. All but one of the patients had ascites; five (26.3%) required drainage of the ascites using a pigtail catheter. Eleven patients (57.9%) had pleural involvement — four (21.0%) with unilateral pleural effusion and seven with bilateral pleural effusion (36.8%). Ten patients (52.6%) experienced dyspnoea, 14 (73.6%) abdominal pain, 10 (52.6%) nausea, and three patients (15.8%) developed generalized oedema. Temperatures above 37 °C were recorded in 14 patients (73.6%), and persisted for 1 to 14 days (Table 2).

The course of the values for the leukocyte count, hemoglobin, hematocrit, and creatinine showed significant differences between the day of admission and the day of discharge; however, no significant differences were observed between the admission and discharge values for platelets, human chorionic gonadotrophin (hCG), estradiol, progesterone, total protein, C-reactive protein (CRP), or liver enzymes (Table 3).

Seven patients (36.8%) had preterm deliveries, six patients (31.5%) had cesarean sections, and four patients (21.0%) had preterm delivery by cesarean section (Table 4). Two patients, both with severe OHSS, developed complications due to bleeding. Two patients (10.5%; one with moderate OHSS and one with severe OHSS) reported a family history of thromboembolism. The patient with severe OHSS had a jugular vein thrombosis, and the pregnancy was terminated due to worsening problems (see the case report below).

Table 1

Comparison of Parameters in Relation to the Severity of Ovarian Hyperstimulation Syndrome in 19 Patients

	I	II	III
Patients	1 (5.3%)	7 (36.9%)	11 (57.9%)
Age (years)	29	30–37	27–41
Stay in hospital (days)	4	6–12	11–33
Early onset OHSS	0	2 (10.5%)	4 (21.0%)
Late onset OHSS	1 (5.2%)	5 (26.3%)	7 (36.8%)
Time from embryo transfer (days)	26	9–14	2–20
Intermediate care (patients)	0	4 (21.0%)	9 (47.3%)
Intermediate care (days)	0	2.7	5.3

Note: OHSS = ovarian hyperstimulation syndrome.

I = mild OHSS; II = moderate OHSS; III = severe OHSS.

Table 2

Diagnostic and Therapeutic Parameters in Relation to the Severity of Ovarian Hyperstimulation Syndrome in 19 Patients

	I		II		III	
	N	%	*n*	%	*n*	%
Dopamine	—		2	10.5	5	26.3
Furosemide	—		2	10.5	9	47.3
Ascites drainage	—		1	5.3	4	21.0
Unilateral pleural effusion	—		—		4	21.0
Bilateral pleural effusion	—		3	15.8	4	21.0
Abdominal pain	—		3	15.8	11	57.9
Dyspnoea	—		3	15.8	7	36.8
Nausea	—		3	15.8	7	36.8
Oedema	—		—		3	15.8
Temperature > 37 °C (patients)	—		4	21.0	10	52.6
Temperature > 37 °C (days)	—		1–5		2–14	

Note: OHSS = ovarian hyperstimulation syndrome.

I = mild OHSS; II = moderate OHSS; III = severe OHSS.

Case Report

A 35-year-old patient presented with severe late-onset OHSS 12 days after oocyte retrieval and 10 days after the transfer of two embryos. She had a history of secondary infertility due to male subfertility and had undergone five ICSI treatments within 2 years, with one miscarriage and one living child born without OHSS developing.

The patient presented with abdominal pain, nausea, and mild shortness of breath. She had an uneventful medical history, but there was a family

https://doi.org/10.1375/twin.9.5.691 Published online by Cambridge University Press

Table 3

Serological Parameters on the Day of Admittance (A) in Comparison with the Day of Discharge (D) in 19 Patients with Ovarian Hyperstimulation Syndrome

	Leukocytes (µL)		Hemoglobin (dL)		Hematocrit (%)		Creatinine (mg/dL)	
	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge
OHSS I	8.800	9.200	12.7	13.6	36	39	1.24	0.62
OHSS II	17.900	17.200	14.6	12.6	42	37	0.62	0.54
	14.200	11.500	15.4	13.2	44.2	37	1	0.7
	13.700	6.300	14.8	11.8	42.3	33.8	1	0.78
	15.400	8.210	17.4	11.4	51.2	33.7	0.74	0.69
	13.100	9.970	14.5	12	44.1	34.8	0.83	x
	23.400	11.000	17.2	12.3	47.8	35.9	0.94	0.67
	16.200	10.400	16.1	12	47.3	35	0.78	0.62
OHSS III	16.300	12.600	14.7	11.5	42	34	0.8	0.54
	9.600	8.100	13.5	12.4	39.6	36	0.66	0.56
	12.500	12.700	13.3	11.5	37.7	33	0.62	0.44
	29.800	9.500	18.1	10.3	49.8	28.9	1.05	0.56
	21.800	8.200	15.3	11.5	42.9	35	x	x
	15.000	10.300	16.8	11.9	49	34	1.02	0.8
	13.800	11.100	14	12.7	39.2	37.4	1.45	0.89
	21.300	15.600	15.9	14.3	45.9	41.6	0.74	0.83
	18.100	13.400	14.7	12.3	41.4	34.7	0.76	0.65
Case report	16.900	8.330	17.4	11.4	47.6	35.2	0.91	0.78
	17.300	6.230	15.9	9.86	47	29	1.13	0.63
OHSS I (range)	8.800–29.800	6.300–17.200	12.7–18.1	9.86–14.3	36–51.2	28.9–37.4	0.62–1.45	0.54–0.89
OHSS II (range)	13.100–23.400	6.300–17.200	14.5–17.4	11.4–13.2	42–51.2	33.7–37	0.62–1	0.54–0.78
OHSS III (range)	9.600–29.800	6.230–15.600	13.3–18.1	10.3–14.3	37.7–49.8	28.9–41.6	0.66–1.45	0.54–0.89
Mean	16.584	10.518	15	12	44	35	1	1
SD	4940.115064	2887.335525	1.519233	1.039580	4.257851	2.959354	0.222769	0.120888
p	> .0001		> .0001		> .0001		> .0001	

Note: OHSS = ovarian hyperstimulation syndrome; x = missing values. I = mild OHSS; II = moderate OHSS; III = severe OHSS.

history of thromboembolism (the patient's father had a venous thrombosis under the age of 40 and another venous thrombosis, a heart attack and a pulmonary thromboembolic event later in life), although she herself had no evidence of thrombophilic markers. Both pleural and pelvic ascites were evident. The ovaries were enlarged. Hematocrit, CRP, and leukocyte levels were all elevated. Platelets, sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT) and creatinine were in the normal ranges, whereas albumin and protein were low.

She received the standard treatment, consisting of intravenous hydration with crystalloids and hydroxyethyl starch, anticoagulation, and monitoring of urine output. Both increasing hCG values and transvaginal ultrasonography were indicative of an intrauterine twin pregnancy. Further ultrasound examination showed declining ascites and pleural effusions. The patient felt well and was discharged 10 days after admission. She received anticoagulation treatment with LMWH for another week.

One day after the patient stopped taking her anticoagulation medication, she presented again with a thrombosis of the internal jugular vein and was treated with LMWH (dalteparin) for anticoagulation, at 2 × 7500 IU/d. The diagnostic work-up for thrombophilia and antiphospholipid antibodies showed a heterozygotic mutation in the *MTHFR* gene (C677T) and a lowered protein S value, but an additional test 1 week later showed that protein S was in the normal range. Diamniotic-dichorionic twins with a regular heartbeat were seen on ultrasound. The patient was transferred to the intensive care unit for further treatment and monitoring.

Despite 11 days of therapeutic anticoagulation with unfractionated heparin (UFH) and LMWH, the thrombosis extended to the right subclavian vein, and a new thrombosis occurred in the left jugular vein. Unexpectedly high doses of UFH were needed to achieve therapeutic ranges in the activated partial thromboplastin time. A weight-adjusted dose regimen of nadroparin resulted in subtherapeutic anti-Xa levels 4 hours after subcutaneous injection. Intravenous injection of nadroparin resulted in similar anti-Xa

https://doi.org/10.1375/twin.9.5.691 Published online by Cambridge University Press

Table 4

Outcome of Twin Pregnancies Complicated by Ovarian Hyperstimulation Syndrome

	I	II	III
Preterm delivery	1	2	4
Cesarean section	1	3	2
Preterm delivery by cesarean section	1	1	2

Note: I = mild ovarian hyperstimulation syndrome (OHSS); II = moderate OHSS; III = severe OHSS.

levels. Therapeutic anticoagulation treatment with UFH was therefore reinstituted on day 12. In addition to the worsening thrombosis, the patient developed a Clostridium difficile infection with diarrhoea.

Eighteen days after the first thrombosis, further treatment options were discussed with the patient. Continuation of the pregnancy with therapeutic anticoagulation rather than pregnancy interruption was recommended, but it was not possible to rule out further risks, including additional thromboembolic incidents. The patient decided in favor of abortion. In the 9th week of gestation (gestational week 8 + 2), abortion was induced with misoprostol (Cytotec 200) vaginally, followed by curettage. A new thrombolic event was ruled out with Doppler ultrasonography when the patient complained of pain in the left leg. The patient received oral anticoagulation (coumarin) for a further 6 months.

Six months later, she was still suffering pain in the right arm. A Doppler ultrasound examination showed that the right jugular and subclavian vein were still completely obliterated. Six months later, oral anticoagulation treatment was stopped, and the patient's heparin turnover was checked by measuring serum anti-Xa. After administration of a weight-adapted dose of LMWH (0.3), the anti-Xa level 4 hours later was 0.35 U/ml (within the normal range), in contrast to the values during OHSS.

She was one of two patients with a positive family history of deep vein thrombosis and was the only patient in whom deep vein thrombosis occurred as a complication of OHSS. No further differences from the other patients were observed (Tables 5 and 6).

Discussion

In the patients with OHSS in twin pregnancies reported here, there was a tendency toward more severe forms of OHSS rather than mild or moderate forms. Moreover, the frequency of late OHSS was more than twice that of early OHSS.

Mathur et al. (2000) investigated the association between pregnancy after IVF/ICSI and OHSS. The authors reported that IVF/ICSI pregnancies were more often associated with late OHSS (with an onset more than 10 days after oocyte retrieval) and with severe OHSS. Multiple pregnancies were significantly more frequent in late OHSS. The authors concluded that as hCG levels tend to be higher in multiple pregnancies from a very early gestational stage, as a result of implantation, the severity of OHSS may reflect a greater magnitude and longer duration of granulosa-cell stimulation in late OHSS as a result of its association with pregnancy. Polycystic ovaries, estradiol values, and oocyte numbers indicated a risk of early OHSS, whereas these parameters were not predictive of late OHSS. Ascites was observed in almost all patients, dyspnoea in 52.6%, nausea in 36.8%, abdominal pain in 73.6%, pleural effusions in 57.9%, and oedema in 15.8%. Abramov et al. (1998) reported ascites in 98.8%, dyspnoea in 95.7%, gastrointestinal disturbances in 57.7%, pleural effusion in 19%, and oedema in 13.5% of patients with severe OHSS.

Twin pregnancies are associated with a risk of thromboembolism; one of the 19 patients in the present study developed a thrombosis (5.2%). Abramov et al. (1998) reported thromboembolism in 2.5% of their study population, with one case of induced abortion (1.5%) due to deterioration of respiratory status and oliguria. In their series, antenatal complications were more common in patients with severe OHSS in comparison with IVF/ICSI pregnancies without OHSS and included pregnancy-induced hypertension, gestational

Table 5

Risk Factors for Ovarian Hyperstimulation Syndrome and Thromboembolism in the Patient Described in the Case Report

Risk factors
Father with a history of thromboembolism
Heterozygotic *MTHFR* mutation (C677T)
Young age
Twin pregnancy
Ovulation induction with hCG
Luteal support with hCG
> 15 oocytes retrieved

Note: hCG = human chorionic gonadotrophin.

Table 6

Course of Parameters in the Patient Described in the Case Report

Course of parameters					
Day after ovulation induction	14	16	19	21	23
Leukocytes	16.9	12.0	9.4	9.9	8.3
Platelets	311	222	299	263	292
Hematocrit	47.6	40.5	35.3	34.4	35.2
Estradiol	4967	3815	5101	x	4917
Progesterone	> 400	229	244	x	226
hCG	76	159	510	x	2513
Albumin	33.5	27.4	x	32.1	x
Creatinine	x	x	x	0.76	x

Note: hCG = human chorionic gonadotrophin; x = missing values.

https://doi.org/10.1375/twin.9.5.691 Published online by Cambridge University Press

diabetes, late intrauterine fetal demise, preterm rupture of membranes, placental abruption, and low birthweight. The authors concluded that antenatal complications in IVF/ICSI pregnancies with OHSS occur significantly more frequently than in IVF/ICSI pregnancies without OHSS. Patients with severe OHSS are exposed to high endogenous oestrogen levels, in addition to cytokines, renin, angiotensin, and possibly prostaglandins, with an unknown effect on early pregnancies. However, these mechanisms do not increase the prevalence of fetal malformations after severe OHSS.

Wiser et al. (2005) compared twin pregnancies after IVF/ICSI complicated by OHSS with twin pregnancies after IVF/ICSI without OHSS. In 64 twin pregnancies with OHSS, the patients were significantly younger and had polycystic ovaries significantly more often than in the control group without OHSS. There were no differences in the incidence of gestational diabetes mellitus, hypertensive disorders, gestational week at delivery, birthweight, or rate of cesarean section. In comparison with singleton pregnancies with OHSS, there was a significantly longer hospitalization period and a higher risk of ovarian torsion in twin pregnancies (10.9% vs. 3%).

In the patients included in the present study, two women with OHSS and twin pregnancies reported bleeding in early pregnancy (10.5%). The values and ranges for leukocytes, hemoglobin, hematocrit, platelets, estradiol, progesterone, and even hCG in patients with twin pregnancies in the present study were comparable to those in patients with singletons.

Pinborg (2005) reported similar risks in IVF/ICSI and control twins with regard to birthweight, gestational age, and the incidence of small-for-gestational-age children. Cesarean section rates, including the frequency of emergency cesarean operations and the rate of vacuum extractions, were higher in IVF/ICSI twin pregnancies than in twin pregnancies without assisted reproduction techniques. It is likely that the slightly higher risk of neonatal intensive care unit admittance in IVF/ICSI twins is due to greater precautions being taken in the highly valued IVF/ICSI twin pregnancies.

The risk of developing a thrombosis during pregnancy is 20 to 40 times lower than the risk of OHSS combined with a pregnancy (Ray & Chan, 1999). Venous thromboembolisms in pregnancy are usually located in the lower extremities, with 70% of cases occurring in the ileofemoral region (Kyrle & Eichinger, 2005). In OHSS patients, however, 60% of thromboembolic events in the 97 cases reported in the literature to date were located in the upper part of the body, with 67% to 75% being venous and 25% to 33% arterial. Thromboembolism in the jugular vein occurs on average 43 ± 30 days after ovulation induction (Delvigne & Rozenberg, 2003). In the patient described above, the first thrombosis occurred on day 31 after the induction of ovulation with hCG. It is not known why OHSS appears to lead to a predilection for thromboembolism developing in the upper part of the body. In a total of 21 cases reported up to 2003, only two patients developed a bilateral jugular vein thrombosis (Delvigne & Rozenberg, 2003). In cases of thrombosis, 85% of the affected patients were pregnant and 75% had OHSS. Hypercoagulopathy correlates positively with high estrogen levels, immobilization, high hematocrit levels, increased intra-abdominal pressure (ascites, enlarged ovaries) and lowered tone in the venous system due to high levels of progesterone in pregnant OHSS patients (Pinborg, 2005; Pinborg et al., 2004). The incidence is therefore likely to be even higher in twin pregnancies with OHSS.

Eighty-five per cent of patients with OHSS have one or more elevated markers of thrombophilia (Binder et al., 2004). Rao et al. (2005) reported that a patient with a jugular vein thrombosis had a possible protein S deficiency, but no family history of thromboembolism, whereas in the patient described here, there was a family history of thromboembolism and a temporary decrease in protein S, combined with a heterozygous C677T mutation.

Unfortunately, thrombosis may occur despite appropriate management and even when prophylactic anticoagulation is administered (Hignett et al., 1995). This may result from heparin-induced antibodies leading to a highly specific and paradoxical form of thrombocytopenia that promotes thrombosis rather than bleeding. Data from pregnant women without OHSS (Barbour et al., 2004; Ensom & Stephenson, 2004; Sephton et al., 2003) show that the pharmacokinetics of LMWH are markedly altered, resulting in lower peak and trough levels. This may lead to treatment failures in pregnancy, with or without OHSS. Close monitoring of anti-Xa levels and thrombus progression can therefore be recommended. In patients who experience thrombotic events despite adequate anticoagulation therapy, heparin-induced thrombocytopenia should be ruled out.

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