The Outcome of In-Vitro Fertilization/Intracytoplasmic Sperm Injection (IVF/ICSI) Cycles Complicated by Moderate-Severe Ovarian Hyperstimulation Syndrome (OHSS)

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Abstract:
A retrospective study was used in the Fertility Clinic of the Department of Obstetrics & Gynecology, Tawam Hospital, Al Ain, Abu Dhabi, United Arab Emirates to determine the outcome of IVF/ICSI cycles complicated by OHSS.

Materials & Methods: In the period between January 1994 and August 2000, 3174 IVF/ICSI cycles were performed and 2918 cycles had reached embryo transfer, 564 women achieved pregnancy (19.33%). 92 women (3.15%) developed moderate-severe OHSS and were hospitalized and their medical and IVF records were reviewed. Supportive management whilst waiting for the condition to resolve spontaneously together with follow-up by ultrasound scan and blood tests was applied to all patients included in the study. Pregnancy test was performed 17 days after ovum pick-up.

Results: Ninety-two women developed moderate-severe OHSS, 37 women of them had a clinical pregnancy (40.2%). 51.4% were singletons and 48.6% were multiple pregnancies; including 13 sets of twins, 4 sets of triplets and one set of quadruplets. The miscarriage rate was 32.4% and the spontaneous fetal reduction rate was 16.6%. 25 women continued pregnancy (67.6%); eleven women had preterm delivery (44%), low birth weight rate was 44% and take home baby rate was 59.4%. The Cesarean section rate was 24%. Pregnancy-induced hypertension rate was only 8% and gestational diabetes 4%. There were no cases of ectopic pregnancy or placental abruption.

Conclusion: The pregnancy rate and the rate of multiple pregnancy, miscarriage, prematurity, low birth weight and Cesarean section rate are significantly higher than those reported previously for pregnancies conceived with the use of assisted reproductive techniques without the development of OHSS. The incidence of other obstetric complications such as pregnancy-induced hypertension, gestational diabetes, abruptio placentae and ectopic pregnancy are not significantly different.

Key words: OHSS, ovarian hyperstimulation syndrome, IVF/ICSI cycles, in-vitro fertilization/ intracytoplasmic sperm injection cycles, pregnancy outcome.

Introduction:
Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of supraphysiological ovarian stimulation, with a varied spectrum of clinical and laboratory manifestations. It is an important side effect of treatment with fertility drugs including gonadotrophins and gonadotrophin-hormone-releasing hormone and less commonly clomiphene citrate. The reported incidence of OHSS for IVF cycles varies between 0.6 and 14% (1). A recent analysis of ten years identified a rising incidence of this syndrome and suggested the existence of an epidemic of this complication (2). Assisted conception treatment, even in the absence of ovarian hyperstimulation syndrome, is associated with supraphysiological ovarian stimulation resulting in oestradiol levels greater than those in natural conception cycles. OHSS is more likely to occur in treatment cycles with the highest ovarian response to stimulation (3). The precise pathogenesis of this syndrome remains to be elucidated. Evidence supports a role of immune system activation, mediated by release of cytokines and vasoactive substances (4). The pathophysiology of OHSS involves increased vascular permeability, loss of fluid into the third space and intravascular dehydration. OHSS is a threat to every woman undergoing ovulation induction and is potentially lethal in its severest form (5). In critical cases there may be thromboembolism, renal failure, and adult respiratory distress syndrome with electrolyte imbalance (6). OHSS associated adverse pregnancy outcome has been reported by several authors (7,8) although others observed no significant difference in miscarriage rate and pregnancy outcome between cycles with OHSS and contemporaneous controls without OHSS (9,10).

This study was designed to observe the outcome of IVF/ICSI cycles complicated by moderate-severe OHSS at Tawam Hospital Fertility Clinic.
Materials and Methods:

During the period of this study from January 1994 to August 2000, 3174 IVF/ICSI cycles were performed at Tawam Hospital Fertility Clinic, 2918 women had reached embryo transfer. 564 women had a clinical pregnancy (19.33%). 92 women (3.15%) developed moderate-severe OHSS who were hospitalized and included in this study.

Information on the age of patients, causes of infertility and its duration, predisposing factors for OHSS, as well as methods used to define moderate-severe OHSS (clinical, laboratory and sonographic methods) were identified by reviewing the patient’s medical and IVF records. Patients with moderate OHSS are those presenting with increasing abdominal discomfort accompanied by nausea, vomiting and/or diarrhoea, ultrasound evidence of ascites with ovarian size ranging between 8-12 cm. Patients with severe OHSS present, in addition to the previous presentation, with clinical ascites possibly with hydrothorax, hemoconcentration, hypovolemia, increased blood viscosity, electrolyte disturbance, decreased renal perfusion, hypoproteinemia and the ovarian size is usually over 12 cm.

Conservative management, including supportive measures waiting for the condition to resolve spontaneously, was applied to all patients included in the study together with follow-up by ultrasound scan and blood tests and drainage of ascites which was required by some patients. Pregnancy test was performed 17 days after ovum pickup. Patients who had a clinical pregnancy diagnosed by identification of a gestational sac were followed to know the pregnancy outcome including the miscarriage rate, spontaneous fetal reduction, multiple pregnancy rate, preterm delivery and low birth weight in addition to other obstetric complications.

Results:

Ninety-two women developed moderate-severe OHSS in the study (3.15%) and were hospitalized. Seventy five women had severe OHSS (81.5%), and 17 women were diagnosed with moderate OHSS (18.5%). Women with moderate OHSS presented with abdominal discomfort, nausea and vomiting together with an ultrasound finding of ascites and enlarged ovaries of 8-12 cm. All cases of severe OHSS presented, in addition to the previous features, with clinical ascites, and oliguria. Sixty per cent of them had hydrothorax in addition to the laboratory and sonographic findings of severe OHSS. Ovarian size was >12cm. The mean age of the women was 29.4 years. Causes of their infertility were polycystic ovarian syndrome (PCO) 40.5%, tubal factor infertility and male factor infertility (27% for each), anovulation 5% and unexplained infertility 0.5%. The mean duration of infertility was six years. The most common predisposing factor identified for OHSS was PCO 40.5%, followed by previous history of OHSS 19%.

Thirty-seven women had a clinical pregnancy (40.2%) and the pregnancy outcome was sought: nineteen (51.4%) had a singleton gestation and 18 (48.6%) were pregnant with multiple gestation including 13 sets of twins (35%), four sets of triplets (10.8%) and one of quadruplets (2.8%).

Twelve women (32.4%) had a miscarriage; eight (21.6%) in the first trimester and four (10.8%) in the second trimester (Tables 1 & 2).

Table 1: Pregnancy Wastage in OHSS-values are given as n (%) or n/n total (%).

<table>
<thead>
<tr>
<th>OHSS Pregnancies (n=37)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage</td>
<td>12</td>
</tr>
<tr>
<td>&lt; 12 weeks</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 12 weeks</td>
<td>4</td>
</tr>
<tr>
<td>Spontaneous reduction</td>
<td>3/18</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>0</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 2: The pregnancy outcome in multiple gestation (n=18)

<table>
<thead>
<tr>
<th>Twins (n = 13)</th>
<th>Triplets (n = 4)</th>
<th>Quadruplet (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>+ Preterm delivery</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>* Low birth weight</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Term delivery</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

Three cases had spontaneous fetal reduction (16.6%). Twenty-five women continued pregnancy (67.6%); of whom eleven had preterm delivery (44%); nine of them were multiple gestations (Table 2). Low birth weight rate (< 2500 gm.) was (44%) and low birth weight ranged between 760-2200 gm. The Cesarean section rate was 24% (16 cases). Other obstetric complications such as pregnancy-induced hypertension and gestational diabetes were 8% and 4% respectively. There were no cases of ectopic pregnancy or abruptio placenta.

OHSS was found to be more common in pregnancy than non-pregnancy cycles (40.2% in OHSS cycles compared to 19.33% for all cycles).
The pregnancy rate, multiple pregnancy, miscarriage, spontaneous fetal reduction, prematurity, low birth weight and Cesarean section rates were significantly higher (p<0.01) than those reported previously for pregnancies conceived with the use of assisted reproductive techniques without ovarian hyperstimulation syndrome. Other obstetric complications were not found to be significantly different.

Discussion:

The reported outcomes of IVF/ICSI cycles complicated by moderate-severe OHSS varies between authors from being poor to good. It is clear that there are theoretical grounds for expecting an association between OHSS and adverse pregnancy outcome. However, the literature on this subject is limited and does not enable a definite conclusion to be drawn.

Several authors have reported an adverse pregnancy outcome in IVF cycles complicated by OHSS including higher miscarriage rate, spontaneous fetal reduction, multiple pregnancy rate, low birth weight and preterm delivery.

Capsi et al noted a higher incidence of miscarriage in human chorionic gonadotrophin cycles in which OHSS occurred compared with those in which OHSS did not occur. High miscarriage rate was also reported by Schenker, and Weinstein and Rabau et al. Similar findings were identified in our study.

The incidence of obstetrical complications including pregnancy-induced hypertension, gestational diabetes, ectopic pregnancy and abruptio placentae were not found significantly different in our study from IVF/ICSI pregnancies without OHSS. Similar findings were found by Schenker JG while Abramov Y et al found an increase in obstetrical complications in pregnancies complicated by OHSS. Chen et al observed no significant difference in miscarriage rate and spontaneous fetal reduction between cycles with OHSS and those without OHSS. Similar findings were observed by Mathur and Jenkins, who also found a higher incidence of multiple pregnancies and preterm labor although the difference was not statistically significant. At least part of the observed higher incidence of low birth weight and prematurity in OHSS pregnancies in our study could be related to the higher incidence of multiple pregnancies in this group.

Patients with PCO are more likely to demonstrate an exaggerated response to gonadotrophin stimulation, placing them at a higher risk of OHSS. They are also more likely than women without PCO to miscarry following assisted conception treatment without the use of gonadotrophin-releasing hormone agonists. The high incidence of miscarriage observed in our study may be partly contributed to the high number of patients with PCO found in our study; a common problem in this part of the world.

This pregnancy outcome observed in our study may provide another argument in favor of the shift away from maximum ovarian stimulation by providing a more “gentle” stimulation regimen that does not aim to maximize ovarian response in every treatment cycle, with the objective of providing a more physiological milieu and reducing the short and long term risks of supraphysiological ovarian stimulation. It is important to identify women at risk of ovarian hyperstimulation syndrome such as PCO diagnosis before ovarian stimulation is initiated as those patients are more likely to develop moderate-severe ovarian hyperstimulation syndrome.

OHSS is a life-threatening condition. Efforts to prevent this syndrome have been tried but the syndrome cannot be completely eliminated. Several authors have reported some preventive methods for this lethal condition.

Conclusion:

The outcome of pregnancies complicated by moderate-severe OHSS is worse than that of assisted conception pregnancies without OHSS including higher miscarriage, spontaneous fetal reduction, multiple pregnancy, preterm delivery, low birth weight and Cesarean section rates, although the pregnancy rate was found to be higher than that reported for IVF/ICSI cycles without OHSS. Other obstetric complications such as pregnancy-induced hypertension, gestational diabetes, abruptio placentae and ectopic pregnancy were not significantly different from assisted conception cycles without OHSS.

Further studies are required in this field by comparing assisted conception pregnancies complicated by OHSS with appropriately matched controls.

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References:


