ARTICLE

Adverse obstetric outcome for the vanishing twin syndrome

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Abstract The aim was to compare obstetric outcomes of IVF singleton pregnancies diagnosed with vanishing twin (VT) syndrome with those pregnancies originating as singleton pregnancies and with twin pregnancies. In this case control study, 57 patients diagnosed with VT syndrome were matched and compared with 171 singleton controls and 171 twin controls. Mean gestational age was 35.1 ± 3.7 versus 38.2 ± 2.6 weeks (P = 0.001) for patients and singleton controls respectively. Birth weights were 2834.4 ± 821.2 versus 3036 ± 489.3 g (P = 0.02), proportion of low birth weight (<2500 g) was 33.3 versus 11.7% (P = 0.0001) and very low birth weight (<1500 g) 3.5 versus 0.6% for patients and singleton controls respectively. The proportion of deliveries before 28 weeks of gestation was 7.0 versus 1.2% (P = 0.01) for patients and singleton controls respectively. When comparing the study group to twin control pregnancies, a similar gestational age at delivery (35 weeks) and rate of preterm birth (23%) were found. In conclusion, pregnancies diagnosed with the VT syndrome after IVF carry a higher rate of adverse obstetric outcomes in terms of preterm deliveries and lower birth weight, compared with IVF pregnancies that were originally singleton. Additionally, significant similarities were observed in the obstetrics outcome of vanishing twin pregnancies and twin pregnancies.

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KEYWORDS: adverse obstetric outcomes, spontaneous reduction of twin, twin pregnancies, vanishing twins

Introduction

The ‘vanishing twin’ (VT) syndrome, defined by the early gestational loss of one of a pair of twins, has been a subject of interest in the literature since its description by Levi (1976). The disappearance of gestational sacs or embryos after demonstrating fetal heart activity by transvaginal sonography in multiple pregnancies is not unusual. When it
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occurs, the process is known as the VT phenomenon. It was proved to be a real clinicopathological entity by Jauniaux et al. (1988), and with the improvement of diagnostic tools, namely transvaginal ultrasound, the frequency of diagnosis of this syndrome has increased, and is reported to be in the range of 12—30% in assisted reproductive conceptions (Pinborg et al., 2005; van Oppenraaij et al., 2009). Sampson and de Crespigny (1992) evaluated the chance for a fetus in a pair of twins to die in utero, and found it in their study to be 19%, or 11% if ultrasound scan demonstrating twin viability was performed prior to, or after 7 weeks of gestation respectively. Single embryonic loss has also been evaluated by Landy and Keith (1998) for twin gestations achieved by assisted reproduction and found to be 38% after the sonographic diagnosis of two embryos. These authors found that the occurrence of vaginal bleeding in early gestation is a risk factor for the disappearance of a single embryo or a gestational sac. Although the aetiology of this phenomenon remains uncertain, the consequences and the effect on the continuing pregnancy are subjected to debate and disagreement. Pinborg et al. described adverse obstetric and neonatal outcomes of this syndrome (Pinborg et al., 2005, 2007), while La Sala et al. demonstrated similar outcomes to true singleton pregnancies (La Sala et al., 2006).

The aim of this study was to compare obstetric outcomes for neonates born after assisted reproduction conception (IVF/intracytoplasmic sperm injection (ICSI)) beginning as twin conception and delivered as singletons (VT) with neonates born after singleton assisted reproduction pregnancies and with assisted reproduction pregnancies beginning and ending as twins.

Materials and methods

This was a retrospective case control study carried out after institutional review board approval was obtained.

A total of 2545 deliveries of IVF/ICSI treatment cycles between 1999 and 2007 were identified and extracted from a computerized data base. Of those, 1373 deliveries were singleton deliveries and 57 cases of ‘VT’ syndrome were singleton out as the study group. The VT syndrome was defined in cases where two fetal pulses were demonstrated between 6 and 7 weeks and one fetal pulse was demonstrated thereafter, but before 12 weeks of gestation. Inclusion criteria were verified by transvaginal ultrasonography. Women undergoing multifetal pregnancy reduction or monochorionic twins were excluded.

Two control groups were chosen as follows: for each case of the study group, three controls were matched: patients carrying singleton pregnancies achieved by IVF/ICSI, adjusted for age and chronological time of treatment. In all, there were 171 matched singleton deliveries. Additionally, for each case of the study group, three twin-control cases were matched. The twin-control group included patients carrying twin pregnancies achieved by IVF/ICSI resulting in twin deliveries, adjusted for age and chronological time of treatment. In all, there were 171 matched twin deliveries. The decision to match cases and controls was intended to make the study and two control groups as comparable as possible. Matching was performed sequentially, with each case of the study group matched to the three following patients, according to the date of embryo transfer and age. The matching procedure was performed in a blinded fashion by using Excel electronic data sheet formulae.

Data were compared in terms of maternal age, mode of assisted reproduction (IVF/ICSI), number of embryos transferred, gestational age, birth weight and gender.

Gestational age was calculated according to the date of embryo transfer. Preterm delivery was defined as birth occurring at or before 34 weeks of gestation, extreme preterm delivery was defined as birth occurring before 28 weeks of gestational age. Low birth weight was defined as birth weight under 2500 g, and very low birth weight as birth weight under 1500 g. Small for gestational age (SGA) was defined as birth weight below the 10th percentile of curves for singletons, multiples and gender according to the gestational age at delivery (Dollberg et al., 1995; Kramer et al., 2001).

Data are reported using the mean ± SD.

Statistics

The statistical analysis was carried out using the Statistics Package for Social Sciences (SPSS) software package (SPSS Inc., Chicago, IL, USA). Differences between parameters in the different patient groups were evaluated using the Fisher’s exact test and the t-test where appropriate. Differences between proportions were evaluated using the chi-squared test. In order to increase the statistical power of the study, a 1:3 proportion was chosen. A P-value of <0.05 was considered statistically significant.

Results

During the study period, there were 1373 singleton deliveries of pregnancies conceived by IVF/ICSI. Out of those, 57 (4.1%) cases of the VT syndrome were identified.

Maternal characteristics as well as treatment cycle data are summarized in Table 1. Maternal age was matched. No significant differences were observed in gravidity and parity. Treatment cycle data in terms of previous IVF-embryo transfer cycles, the number of embryos transferred and the rate of ICSI (at 40 versus 45 and 42%) for the study group and the controls respectively were similar.

Significant differences for all obstetric parameters evaluated, apart from the rate of SGA newborns and the rate of very low birth weight, were demonstrated for VT versus control singleton pregnancies (Table 2). Gestational week at delivery (P = 0.001) and birth weight (P = 0.02) were lower in the study group compared with controls. The proportion of low birth weight (P = 0.0001), preterm delivery (P = 0.0003) and extreme preterm delivery (P = 0.01) were higher in the study group compared with controls. Out of 57 deliveries in cases of VT, 30 (52.6%) male and 27 (47.4%) female babies were born (weights were controlled according to gender).

No significant differences were observed in gravidity, parity and treatment cycle data in terms of previous IVF-embryo transfer cycles, the number of embryos transferred and the rate of ICSI, for the study group and the twin-control group respectively, as listed in Table 1.
The comparison between the VT pregnancies and the twin-control pregnancies is presented in Table 3. Gestational week at delivery and the proportion of preterm delivery and extreme preterm delivery were similar for the study group and the twin-control group. Birth weight was significantly lower for the twin-control compared with the study group (P = 0.001). The rate of low birth weight (<2500 g) was significantly higher (P = 0.001) in the twin-control group (67.0%) compared with the study group (33.3%); however, the rate of very low birth weight (<1500 g) was not significantly different, being 3.5% for the study group and 8.5% for the twin-control group. Interestingly, the proportion of small for gestational age was significantly higher (P = 0.03) in the VT pregnancies (14%) compared with twin pregnancies (6%).

Discussion

This case-control study compared the perinatal outcome of assisted reproduction pregnancies of the VT syndrome with that of assisted reproduction singletons. It was found that pregnancies diagnosed with the VT syndrome carry a higher rate of adverse obstetric outcomes. Moreover, the obstetric outcomes of the VT pregnancies in certain aspects, such as gestational age at delivery and the rate of preterm deliveries, were found to be similar to twin pregnancies.

The present study found that 4% of singleton deliveries after assisted reproduction treatment originated in twin pregnancy. This figure is similar to 6% reported by Shebl et al. (2008). Other groups have reported higher rates (up to 30%) of single embryonic loss in pregnancies commencing with twins (Sampson and de Crespigny 1992; Pinborg et al., 2005, 2007).

Regarding the obstetric outcomes of pregnancies diagnosed with the VT syndrome, the data support conclusions made by others and reviewed recently (van Oppenraaij et al., 2009). This review, performed on behalf of the European Society for Assisted Reproduction and Embryology Special Interest Group for Early Pregnancy (SIGEP), demonstrated an increase in adverse obstetric outcome after the VT/triplet phenomenon. It was postulated that this might be due to early implantation crowding, resulting in an unfavourable implantation site with uteroplacental insufficiency. It is of note, however, that when comparing the present work with that of others, different definitions have been used for preterm delivery. While in the present study it was defined as birth occurring before 34 weeks gestational age, others defined it as earlier than 37 weeks (Pinborg et al., 2005; Shebl et al., 2008), and while extreme preterm delivery is defined here as birth occurring earlier than 28 weeks gestational age, others have defined it as earlier than 34 weeks (Shebl et al., 2008) or 32 weeks (Pinborg et al., 2005). Shebl and co-authors demonstrated a higher risk for lower birth weights and small for gestational age newborns in singleton deliveries of VT pregnancies in a study of 46 cases (Shebl et al., 2008). Mean birth weight of 2876 versus 3249 g (P = 0.0004) were demonstrated for cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group, n = 57</th>
<th>Singleton controls, n = 171</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age years</td>
<td>32.8 ± 5.1</td>
<td>32.4 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Previous IVF/embryo transfer cycles</td>
<td>3.3 ± 2.6</td>
<td>3.8 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.8 ± 1.3</td>
<td>2.4 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>1.6 ± 0.5</td>
<td>1.9 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>2.5 ± 0.5</td>
<td>2.6 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Rate of ICSI n (%)</td>
<td>23 (40.4)</td>
<td>77 (45.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD, unless otherwise stated. ICSI = intracytoplasmic sperm injection. There were no statistically significant differences between the study and control groups.
and controls respectively. A significant proportion of low birth weights (under 2500 g) and SGA newborns were also demonstrated in a large cohort (n = 642) of survivors of the VT phenomenon (Pinborg et al., 2007). They concluded that IVF singletons from VT gestations have a higher risk of being SGA than singletons from a single gestation and that the higher the gestational age at the time of vanishing, the higher the risk that the surviving newborn will be SGA. Previous work performed by the same group (Pinborg et al., 2005) demonstrated worse short and long-term sequelae of survivors of this syndrome, namely a 3.6-fold higher rate of mortality in survivors and (although not statistically significant) a two-fold increase in the prevalence of cerebral palsy. The above perinatal results are similar to the perinatal results of twin gestation in general. A higher perinatal mortality (Gee, 1992; Wimalasundera et al., 2003) and cerebral palsy rate (Petterson et al., 1993) are observed in twin pregnancies. Interestingly, VT pregnancies are closer in their obstetric outcome to twin pregnancies regarding gestational age at delivery (35 weeks for both groups) and the rate of pre-eclampsia (Chasen et al., 2006). Trophoblast insufficiency may explain the poorer obstetric outcomes described above.

Indirect support for this suggested explanation is provided by the finding of Cheang et al. (2007) that high-order multiple pregnancies after fetal reduction are still associated with a increased risk of premature delivery and low birth weight when compared with non-reduced twin pregnancies (Chasen et al., 2006; Groutz et al., 1996). The comparison between selectively induced reduction of one embryo and the VT pregnancies is interesting and implicit of a common pathway for both phenomena. It raises an assumption that the fate of a pregnancy in terms of the placental function, and the time of delivery is determined in its early stage, by the number of embryos implanted. Events like spontaneous vanishing of a twin or induced reductions do not radically change what was previously programmed.

However, timing of co-twin demise may be an important factor in determining the outcome of the VT pregnancy. Unfortunately these data are not available. Others (Pinborg et al., 2005) have found that obstetric risks increased, the later in pregnancy spontaneous reduction occurred, and were almost entirely due to spontaneous reductions at >8 weeks gestation. If spontaneous VT and induced fetal reduction share a common pathophysiological mechanism for adverse obstetric outcome, then according to the above findings by Pinborg et al., it will be of value to perform induced reduction as soon as possible. However selective fetal reduction is usually performed between 10 and 13 weeks of gestation for technical reasons (e.g. the fetuses have to be large enough for adequate visualization by transabdominal ultrasound), because most spontaneous fetal losses will have occurred by then, and to obtain results of the survey of the fetal anatomy for structural anomalies, chorionic villus sampling or nuchal translucency. The transvaginal reduction approach, which can be easily performed earlier in pregnancy, has been found to be associated with increased post-procedural pregnancy loss rates (Evans et al., 1994). Support for the above explanation is given by the results of the comparison between VT pregnancies and twin pregnancies. Interestingly, VT pregnancies are closer in their obstetric outcome to twin pregnancies regarding gestational age at delivery (35 weeks for both groups) and the rate of

### Table 3 Perinatal outcome data of the study group and the twin controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group, n = 57</th>
<th>Twin-controls, n = 171</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational week</td>
<td>35.1 ± 3.7</td>
<td>35.3 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2834.4 ± 821.2</td>
<td>2235.8 ± 549.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Low birth weight&lt;2500 g</td>
<td>19 (33.3)</td>
<td>229 (66.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preterm delivery&lt;34 weeks of gestation</td>
<td>13 (22.8)</td>
<td>40 (23.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Very low birth weight&lt;1500 g</td>
<td>2 (3.5)</td>
<td>29 (8.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Delivery before 28 weeks of gestation</td>
<td>4 (7.0)</td>
<td>12 (7.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Small for gestational age&lt;10th percentile</td>
<td>8 (14.0)</td>
<td>21&lt; (6.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%); NS = not statistically significant.

- Birth weight <2500 g.
- Delivery before 34 weeks of gestation.
- Birth weight <1500 g.
- Birth weight below the 10th percentile according to gestational age at delivery.
- Out of 342 newborns.
preterm deliveries (23 and 7% for preterm delivery and extreme preterm delivery respectively for both groups), than to singleton pregnancies. However in terms of birth weights, the VT group results (2834 g) are in the middle between twin pregnancies (2235 g) and singleton pregnancies (3036 g). Those results support the hypothesis that the time of delivery is determined in early stage, by the number of embryos implanted, and birth weight is influenced to a lesser degree.

In conclusion, although the aetiology remains obscure and different pathophysiological mechanisms have been proposed, the VT syndrome is by no means a rare occurrence in pregnancies conceived following assisted reproduction treatment.

In this work, it was demonstrated that pregnancies diagnosed with this syndrome have worse obstetric outcomes. Earlier gestational age at delivery as well as lower birth weights and a significantly higher rate of LBW and VLBW neonates were found in the study group of patients with the VT syndrome as compared with singleton deliveries conceived by assisted reproduction. Additionally, significant similarities were observed in the obstetric outcome of VT pregnancies and twin pregnancies.

References


Declaration: The authors report no financial or commercial conflicts of interest.

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