Risk of spontaneous abortion in singleton and twin pregnancies after IVF/ICSI

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BACKGROUND: The risk of spontaneous first trimester abortion is estimated to be between 10 and 20%. Although it is common knowledge that the incidence of abortion decreases as pregnancy progresses, exact data in relation to the duration of pregnancy are scarce. METHODS: We reviewed 1597 clinical IVF/ICSI pregnancies with known outcome and tabulated the number of miscarriages or fetal demise per intervals of 2 weeks. We furthermore compared the outcome in terms of fetal survival of 1200 singleton pregnancies with that of 397 twin pregnancies. RESULTS: The overall incidence of non-ongoing singleton pregnancies was 21.7%. Fetal death, after positive heart activity had been recorded, occurred in 12.2% of singleton pregnancies. The overall incidence of spontaneous abortion in twin pregnancies was 17.1% (12.1% vanishing twins and 5.0% complete miscarriages). The incidence of miscarriage in the twin pregnancies, expressed per gestational sac, was 11.1%. Once fetal heart activity was present, the risk of abortion (per gestational sac) was 7.3%, which is significantly lower than that in singleton pregnancies. CONCLUSIONS: Our data give an estimate of the probability of miscarriage or fetal demise at any given period of the first trimester both for singleton and twin pregnancies. Twin pregnancies after IVF have a better potential for survival than singleton pregnancies.

Key words: abortion/ICSI/IVF/singleton/twin

Introduction

The incidence of first trimester abortion is estimated to be between 10 and 20%. The true incidence, however, is not well known because many abortions occur before pregnancy is clinically recognized. Data from spontaneous pregnancies are difficult to ascertain because this would necessitate the systematic follow-up of a large consecutive cohort of women by determination of hCG and by ultrasound. In contrast, after infertility treatment and particularly following IVF treatment, the diagnosis of pregnancy is made at an early stage and most women are motivated to have their pregnancy followed up very closely.

There are no solid data to compare the incidence of miscarriage in spontaneous versus IVF pregnancies but it is generally accepted that the incidence is slightly higher after IVF (Ezra and Schenker, 1995; Simon et al., 1999). The main reason for a higher incidence is the age of the patients, which on average is 3–5 years higher than that of a fertile population at the time of a first pregnancy. Indeed, studies on the risk of spontaneous miscarriage indicate that maternal age is an important risk factor (Andersen et al., 2000). There is clear evidence from oocyte donation programmes that this risk is associated with the ageing of the oocytes, rather than that of the uterus (Navot et al., 1994; Abdalla et al., 1997). Moreover, studies on oocytes and embryos using the fluorescent in-situ hybridization (FISH) technique have shown that the incidence of aneuploidy in human oocytes increases with age, rising in women aged >35 years and even more so >40 years (Abdalla et al., 1993; Fretts et al., 1995).

Stoeckel (1945) was the first to suggest that twins are more often conceived than born. With the advent of ultrasound, first abdominal and, in the late 1980s, vaginal ultrasound, more detailed information regarding early resorption in multiple gestations became available. Still the true incidence of vanishing twins is difficult to assess. Landy and Keith (1998) reviewed the majority of pertinent studies published since 1990. Most of these studies describe pregnancies conceived as a result of assisted reproductive techniques. Using these data it was estimated that ~30% of these twins will ultimately result in singletons and <10% will end in a complete abortion. When monochorionic twins were compared with dichorionic twin pregnancies (Sebire et al., 1997), the rate of fetal loss was significantly higher in the former. This makes it difficult to extrapolate the findings in assisted reproductive treatment twin pregnancies, where monozygotic twins are rare, to spontaneous twin pregnancies.

In the literature, little information exists on the risk of miscarriage in relation to gestational age and the presence of fetal heart activity (Hill et al., 1991; Frates et al., 1993; Goldstein, 1994). We therefore analysed the outcome of 1200
singleton and 397 twin IVF pregnancies, which were all followed up by transvaginal ultrasound at regular intervals throughout the first trimester. Although the absolute figures may not be representative for the abortion rate in spontaneous pregnancies, we may assume that the relative risk of miscarriage in relation to the duration of pregnancy and the detection of fetal heart activity we obtained from our study in IVF patients can be extrapolated to spontaneous pregnancies.

Also, no large scale studies exist which compare the risk of spontaneous abortion in singleton pregnancies with that in twin pregnancies, taking into account the fate of each gestational sac.

We therefore compared the outcome of singleton pregnancies with twin pregnancies for each gestational sac separately.

### Materials and methods

#### Patients

Records of all IVF/ICSI patients treated in our centre between 1993 and 2000 were reviewed for inclusion in the present study. We included only those patients who were followed in our centre until 12 weeks of gestation and of whom we had reliable information on the outcome of pregnancy.

Out of 2778 pregnancies that were obtained in our infertility department between 1993 and 2000, 1778 (64.0%) were followed up at 2-weekly intervals closely in our centre and had reliable information on the outcome of pregnancy. These pregnancies were analysed: 103 (5.8%) were biochemical, 39 (2.2%) were ectopic and 1636 (92.0%) were clinical. Of the 1636 clinical pregnancies, 1200 were singletons, 397 were twins and 39 were triplets. Only the singletons and twins were further studied.

The indications for infertility as well as the number of embryos transferred were not significantly different between the group with singletons and the group with twins.

#### Definitions and analysis

A pregnancy was defined by the detection of a positive serum hCG (>0.050 IU/ml) 17 days after oocyte retrieval. A biochemical pregnancy was defined as a pregnancy without a intrauterine gestational sac that resolved spontaneously. A spontaneous abortion was defined as either an empty gestational sac (blighted ovum) or fetal demise. Abortion was registered as having occurred on the day that an empty gestational sac or fetal demise was recorded by transvaginal ultrasound, irrespective of the time of expulsion or evacuation by curettage. An ongoing pregnancy was defined as a delivery beyond the 25th week of pregnancy. Proportions were calculated with their 95% confidence intervals (CI). The Z-test was used to compare proportions. \( P < 0.05 \) was considered statistically significant.

#### Results

Of the 1200 singleton pregnancies, 938 (78.2%) were ongoing, yielding an overall incidence of spontaneous abortion of 21.8% (262 spontaneous abortions). After fetal heart activity was detected on ultrasound, the risk of abortion declined to 12.2% (CI: 10.2–14.5%). At 7 weeks this risk decreased to 11.9% (CI: 9.8–14.1%), at 9 weeks to 8.2% (CI: 6.7–10.5%), at 11 weeks it was 4.2% (CI: 2.9–5.7%) and at 13 weeks the risk of miscarrying had dropped to 2.2% (CI: 1.3–3.4%) (Table I, Figure 1).

Of the 397 twin pregnancies, 329 (82.8%) were ongoing, 48 (12.1%) ended with a partial miscarriage (vanishing twins) and 20 (5.1%) ended with a complete miscarriage. The risk of waste of at least one gestational sac in twin pregnancies therefore was 17.2%. When the incidence of miscarriage was calculated for each gestational sac separately, the abortion risk was 11.1% per sac. We also calculated the abortion rate (per gestational sac separately) in relation to the duration of pregnancy. Once fetal heart activity was positive, the risk of abortion was 7.3% (CI: 5.2–9.8%). At 9 weeks gestational age the abortion risk had declined to 4.9% (CI: 3.2–7.2%), at 11 weeks this risk was 2.2% (CI: 1.1–3.9%) and at 13 weeks it was 2.0% (CI: 0.9–3.7%) These results are shown in Table I.

From Figure 1 it can be seen that there is a significantly higher risk of abortion expressed per gestational sac in singleton pregnancies compared with twin pregnancies, at each interval of the first trimester of pregnancy. This difference remains significant until 11 weeks gestational age.

In the group of singleton pregnancies the mean ± SD maternal age was 31.3 ± 0.7 years, while in the twin group the mean maternal age was 30.7 ± 0.6 years. To calculate the age-corrected incidence of spontaneous abortion, we divided the pregnancies into two groups according to maternal age. A first group contained patients ≤35 years of age and in the second

### Table I. Risk of spontaneous abortion per fetal sac in relation to gestational age (comparison of twin pregnancies versus singleton pregnancies)

<table>
<thead>
<tr>
<th></th>
<th>Singleton</th>
<th>Twin</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total risk of spontaneous abortion (%)</td>
<td>21.10</td>
<td>11.10</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>From +ve heart activity onwards (%)</td>
<td>12.20</td>
<td>7.30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After 7 weeks (%)</td>
<td>11.90</td>
<td>7.30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>After 9 weeks (%)</td>
<td>8.20</td>
<td>4.90</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>After 11 weeks (%)</td>
<td>4.20</td>
<td>2.20</td>
<td>NS</td>
</tr>
<tr>
<td>After 13 weeks (%)</td>
<td>2.20</td>
<td>2.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.
group the maternal age was \( >35 \) years. The risk of abortion was calculated for each group (Table II). The difference in miscarriage rate per gestational sac between singleton and twin pregnancies was significant in both age categories. A significant difference was found when miscarriage of women \( \leq 35 \) years of age was compared with the miscarriage rate of women \( >35 \) years. This significant difference was found in both singleton and twin pregnancy groups (Table II).

### Discussion

Our data show that the incidence of abortion in singleton IVF pregnancies drops from an overall high of 21.1–12.2% at 6 weeks gestation, when fetal heart activity is recorded. From 6 weeks onwards, the incidence drops further with 2–4% at an interval of 2 weeks ending with a residual risk of fetal demise at 13 weeks gestation of 2.2%. A similar curve was obtained in twin pregnancies but the incidence of abortion, expressed per gestational sac, was significantly lower than in singleton pregnancies. In both singleton and twin pregnancies, the incidence of abortion increased with age.

Human reproduction is a remarkably inefficient process with a high risk of early fetal wastage. Wilcox et al. (1988) investigated the overall incidence of abortion by collecting daily urine specimens from 221 healthy women who were attempting to conceive. Urinary concentrations of hCG were measured for a total of 707 menstrual cycles. Using a threshold level of 2.5 IU hCG per litre of urine on 3 consecutive days, they found that 22% of pregnancies ended before they could be detected by ultrasound. The overall rate of pregnancy loss, including clinically recognized spontaneous abortions, was 31% (Wilcox et al., 1988).

Numerous causes for this low rate of viable conceptuses can be suggested. It is thought that intrinsic abnormalities within the embryo are the major reason for failed conceptions or early fetal death. The most significant intrinsic factor contributing to embryonic loss is aberrations in the first meiotic division resulting in non-disjunction and aneuploidy. Trisomies 13, 15, 16, 18 and 21 account for the most common autosomal trisomies in spontaneous pregnancy losses (Racowsky, 2002). It may be that in the future preimplantation genetic screening of embryos prior to transfer may reduce early pregnancy wastage resulting from aneuploidy (Handyside et al., 1999; Munné et al., 1999).

In assisted reproduction technology, inappropriate culture conditions may considerably impair human embryonic development in vitro and implantation potential, and it is thought that the improvement in pregnancy rates after assisted repro-

### Table II. Total risk of spontaneous abortion per fetal sac in relation to maternal age

<table>
<thead>
<tr>
<th>Age</th>
<th>Singleton</th>
<th>Twin</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 35 ) years (%)</td>
<td>19.8 (201/1015)</td>
<td>9.5 (67/704)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( &gt;35 ) years (%)</td>
<td>28.6 (59/185)</td>
<td>18.8 (17/90)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.0009</td>
<td>&lt;0.003</td>
<td></td>
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The outcome in terms of survival of twin pregnancies appears to be better than that of singleton pregnancies. Although women with twin pregnancies were somewhat younger than those with a singleton pregnancy, this difference cannot be explained by differences in age. Indeed, when we compare miscarriage rates between singletons and twins in different age groups, the differences between singletons and twins remained in all age groups. In assisted reproduction treatment cycles, it still is a widespread habit to transfer more than one embryo, in order to maximize the chance of a pregnancy. This practice results in a high rate of multiple pregnancies. The incidence of multiple pregnancies after IVF does not, however, follow a binomial probability curve. Twinning rates are much higher than expected. This means that embryos do not implant in an independent way, which is also demonstrated by the results obtained with single embryo transfer (SET). However, all pregnancies in the present study are the result of a strategy of double embryo transfer and no elective SET pregnancies were included in our data (we only introduced SET in our centre in 1999 in a systematic way and on a large scale) (Coetsier and Dhont, 1998; De Sutter et al., 2000; Dhont, 2001). The observation that miscarriage rates per gestational sac are lower in twin than in singleton pregnancies therefore may suggest that embryos in twin pregnancies have a better intrinsic potential than in singleton pregnancies. It would seem that these embryos are part of a better cohort of embryos, not only possessing a higher implantation potential, but also a higher potential for successful further development.

When the complete pregnancy loss in twins (5.1%) was compared with the pregnancy loss in singletons (21.1%) the difference is very significant.

It is clear that the chance of complete pregnancy loss is more than twice as large in the singleton group when compared with the twin group. This means that the embryological potential for successful development is not the same in both groups.
This is congruent with data comparing the outcome of IVF singleton and twin pregnancies with that of spontaneous singleton and twin pregnancies (Dhont et al., 1999).

Because the decision whether a pregnancy was a singleton or a twin could only be made at the moment of the first ultrasound, it can be assumed that a fraction of these singletons were in fact early vanishing twins. This early pregnancy loss might have contributed to further pregnancy loss later on (after the first ultrasound).

Keeping in mind that multiple pregnancies are associated with a significantly higher risk of complications for both mother and child than singleton pregnancies, and given the economic consequences of twin pregnancies for society (ESHRE Capri Workshop Group, 2000; Olivennes, 2000), the results of this study should not be interpreted as a plea for twin pregnancies and double embryo transfer. On the contrary, this study provides additional proof that SET is a logical strategy to consider (Vilska et al., 1999; Gerris and Van Royen, 2000; Martikainen et al., 2001; De Sutter et al., 2002). Indeed, in pregnancies occurring after SET, the embryo which was selected for transfer would have implanted if a double embryo transfer had been performed. This implies that this single embryo leading to pregnancy after SET has the same developmental potential as when it would have been part of a twin pregnancy following a double transfer. It will be very interesting to extend this study in the future to all SET pregnancies, and it is to be expected that the miscarriage rates in SET pregnancies will be as low as those reported for the twins in the present study.

In conclusion, after fetal heart activity is established, the risk of abortion in IVF pregnancies is halved. The potential for survival is significantly higher in twin pregnancies at all stages of the first trimester, pointing to a cohort phenomenon.

References


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