Risks of miscarriage and early preterm birth in trichorionic triplet pregnancies with embryo reduction versus expectant management: new data and systematic review

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BACKGROUND: Triplet pregnancies are associated with a high risk of miscarriage and early preterm birth. It is uncertain if the outcome is improved by embryo reduction (ER). METHODS: We examined trichorionic triplet pregnancies with three live fetuses at 10–14 weeks of gestation that were managed expectantly or by ER. The two groups were compared for the rates of miscarriage, defined as pregnancy loss before 24 weeks, and preterm delivery prior to 32 weeks. In addition, systematic searches were performed to identify studies comparing outcomes in expectant management versus ER in triplet pregnancies. RESULTS: We combined data from 365 pregnancies managed in our centre with those of five previous studies. In total there were 893 pregnancies. In the ER group (n = 482) compared to the expectantly managed group (n = 411), the rate of miscarriage was higher [8.1 versus 4.4%; relative risk (RR) = 1.83, 95% confidence interval (CI) = 1.08–3.16, P = 0.036] and the rate of early preterm delivery was lower (10.4 versus 26.7%, RR = 0.37, 95% CI = 0.27–0.51, P < 0.0001). It was calculated that seven (95% CI = 5–9) reductions needed to be performed to prevent one early preterm delivery, while the number of reductions that would cause one miscarriage was 26 (95% CI = 14–193). CONCLUSIONS: In trichorionic triplets, ER to twins is associated with an increase in the risk of subsequent miscarriage and decrease in risk of early preterm birth.

Key words: embryo reduction/first trimester/nuchal translucency/systematic review/trichorionic triplet pregnancy

Introduction

The incidence of triplet and higher order pregnancies is influenced by use of assisted reproductive techniques and correlates directly with the number of embryos transferred after IVF (Crowther, 1999). This has led to a substantial increase in the incidence of triplet pregnancies over the last 25 years. In the US triplet and higher order multiples birth rates increased from 37 to 184 per 100 000 between 1980 and 2002, although there has been a slight reduction in the rate of increase since 1998 (Martin et al., 2005). Similarly, a decline in triplet pregnancies has been observed in the United Kingdom since 1998 and this probably reflects voluntary and statutory regulation of treatment regimes as well as refinements to assisted reproductive technologies (Simmons et al., 2004). Multifetal pregnancies are known to be associated with a higher risk in maternal, perinatal and long-term complications when compared to singletons or twins (Botting et al., 1987; ESHRE Capri Workshop Group, 2000). For example, in a study in Australia the incidence of cerebral palsy at the age of 1 year was found to be 1.6 per 1000 survivors in singletons, 7.3 in twins and 28 in triplets (Petterson et al., 1993).

There is ample evidence that in high-order multifetal pregnancies, ER is associated with a decrease in the background risk of miscarriage and perinatal death (Evans et al., 2004). However, the issue of whether ER in triplets is beneficial remains controversial (Saugstad, 2003; Blickstein, 2004), and in a previous study comparing triplet pregnancies that underwent ER to those opting for expectant management we showed that neonatal survival rates were similar between the two groups (Papageorghiou et al., 2002).

The two major complications in triplet pregnancies, either managed expectantly or by ER, are fetal loss before 24 weeks and early preterm delivery before 32 weeks. In this study, we compare the incidence of these two complications in 365 trichorionic triplet pregnancies that we managed expectantly or by ER to twins and combine these data with those derived from a systematic review of previous studies reporting on these outcomes.

Materials and methods

Observational study

We examined the outcome of trichorionic triplet pregnancies with three live fetuses demonstrated by ultrasound examination at 10–14 weeks of gestation. All patients were managed in our unit, which is a tertiary referral centre for fetal diagnosis and treatment. Chorionicity
was determined by ultrasonography as previously described (Sepulveda et al., 1996). Parents were counselled regarding the options of expectant management or ER and that the decision should essentially depend on parental preference, because there is no conclusive scientific evidence of medical benefit from ER. All reductions were performed transabdominally by ultrasonic-guided intracardiac potassium chloride injection using a 20-G needle. Maternal details and ultrasound findings were entered into a computer database at the time of the examination and in cases undergoing ER procedure details were also recorded. Pregnancy outcomes were collected into the same database when they became available from the referring hospitals or from the patients themselves.

The rates of miscarriage, defined as pregnancy loss before 24 weeks of gestation, early preterm delivery, defined as delivery prior to 32 weeks of gestation and median gestational age at delivery were calculated for the two groups. In addition the number of surviving fetuses for each pregnancy was compared. Chi-square or Fischer’s exact and Mann–Whitney U-tests were used as appropriate to examine the significance of differences between the two groups for pregnancy outcomes. Significance was assumed at \( P < 0.05 \) and two-tailed \( P \)-values are reported.

**Systematic review**

Independent searches of medical literature databases [The Cochrane Library, Issue 2, 2005, PubMed and Medline (1 July 2005)] were performed by two of the researchers (A.P. and V.B.), in order to identify all studies meeting the following criteria: triplet pregnancies; comparison of data on expectant management versus ER over the same study period; outcomes of pregnancy loss prior to 24 weeks of gestation or early preterm birth prior to 32 weeks of gestation. The database search terms used were ‘triplet pregnancy’, ‘multiple pregnancy’, ‘multifetal’, ‘multi-fetal’, ‘reduction’, ‘abortion’, ‘termination’, ‘fetocide’ and ‘feticide’. In addition references of articles identified were checked for eligibility. Both authors assessed studies for inclusion and any discrepancies were resolved by discussion, or referral to a third author (K.N.).

Studies where there was a difference in gestational age at recruitment between the ER and expectantly managed groups were excluded, as such a difference can influence the apparent rate of pregnancy loss (Evans et al., 2003). After construction of \( 2 \times 2 \) tables for the outcomes of interest, relative risks (RRs), 95% confidence intervals (CIs) and number needed to treat (NNT) or harm (NNH) were calculated. In cases of cells containing zero, 0.5 was added to each cell of the \( 2 \times 2 \) table.

**Results**

**Observational study**

In our centre, between 1986 and 2005, we examined 387 trichorionic triplet pregnancies with three live fetuses at 10–14 weeks of gestation. In 22 pregnancies, ER to one fetus was carried out and these cases were excluded from further analysis. The remaining 365 pregnancies were managed expectantly \((n=185)\) or by ER to two fetuses \((n=180)\) on the basis of parental choice. There was no significant difference in the median gestational age at recruitment between the two groups (median 12 weeks, range 10–14 weeks for both). In those undergoing ER, this was carried out within 3 days of the initial assessment. The characteristics of the pregnancies and pregnancy outcomes are given in Table I.

In the ER group, compared to the expectantly managed group, the rate of miscarriage was higher (8.3 versus 4.9%), the rate of early preterm delivery was lower (9.7 versus 23.9%) and the median gestational age at delivery was higher (36.1 versus 33.8 weeks; Figures 1 and 2). The median interval between assessment and miscarriage or delivery was 6 (range 0–11) weeks and in the expectantly managed group it was 7 (range 5–11) weeks. The overall incidence of pregnancies with no survivors was 8.9% in the ER group, 6.5% in the expectantly managed group.

**Table I.** Maternal and pregnancy characteristics of trichorionic triplet pregnancies managed expectantly or reduced to twins at 12 (10–14) weeks

<table>
<thead>
<tr>
<th></th>
<th>Expectant management (N=185)</th>
<th>Embryo reduction (N=180)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>34.0 (18–44)</td>
<td>33.3 (22–50)</td>
<td>0.646</td>
</tr>
<tr>
<td>Conception ([%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>20 (10.8)</td>
<td>13 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Ovulation induction</td>
<td>29 (15.7)</td>
<td>43 (23.9)</td>
<td>0.096</td>
</tr>
<tr>
<td>IVF</td>
<td>136 (73.5)</td>
<td>124 (68.9)</td>
<td></td>
</tr>
<tr>
<td>Delivery gestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 weeks ([%])</td>
<td>9 (4.9)</td>
<td>15 (8.3)</td>
<td>0.260</td>
</tr>
<tr>
<td>24–31 weeks ([%])</td>
<td>42 (23.9)</td>
<td>16 (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (range)</td>
<td>33.8 (24.0–38.0)</td>
<td>36.1 (25.1–41.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pregnancies with ([%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No survivors</td>
<td>12 (6.5)</td>
<td>16 (8.9)</td>
<td></td>
</tr>
<tr>
<td>One survivor</td>
<td>4 (2.2)</td>
<td>5 (2.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Two survivors</td>
<td>8 (4.3)</td>
<td>159 (88.3)</td>
<td></td>
</tr>
<tr>
<td>Three survivors</td>
<td>161 (87.0)</td>
<td>164 (91.1)</td>
<td>0.636</td>
</tr>
<tr>
<td>At least one survivor</td>
<td>173 (93.5)</td>
<td>21 (11.7)</td>
<td>0.826</td>
</tr>
<tr>
<td>At least one death</td>
<td>24 (13.0)</td>
<td>323 (59.8 or 89.7)</td>
<td>0.735</td>
</tr>
</tbody>
</table>

\( ^a \) Of those that did not miscarry.
\( ^b \) Death: fetal or neonatal death, excluding deaths from reduction and anembryonic pregnancy.

**Figure 1.** Survival curve for gestational age at delivery between triplet pregnancies managed expectantly (solid line) versus those with embryo reduction (ER) (dotted line). Note the higher incidence of miscarriage but later gestation at delivery in the ER group.
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1914–1993; Lipitz et al., 1994; Smith-Levitin et al., 1996; Sebire et al., 1997a; Kadhel et al., 1998; Mansour et al., 1999; Yaron et al., 1999; Leondires et al., 2000; Papageorghiou et al., 2002; Antsaklis et al., 2004; Geipel et al., 2004). However, 12 of the 17 studies were subsequently excluded, and these are summarized in Table II. A meta-analysis combining the data from the remaining five studies with our data included a total of 893 pregnancies. In 482 pregnancies, there was ER to twins and 411 were managed expectantly (Table III).

In the ER group, compared to the expectantly managed group, the rate of miscarriage was higher (8.1 versus 4.4%; RR = 1.83, 95% CI = 1.08–3.16, \(P = 0.036\)) and the rate of early preterm delivery was lower (10.4 versus 26.7%, RR = 0.37, 95% CI = 0.27–0.51, \(P < 0.0001\); Figure 3). It was calculated that seven (95% CI = 5–9) reductions needed to be performed to prevent one early preterm delivery, while the number of reductions that will cause one miscarriage was 26 (14–193).

**Discussion**

The data of our observational study and the systematic review of trichorionic triplet pregnancies suggest that ER to twins increases the risk of miscarriage by about 4%. The interval between ER and miscarriage was more than 2 weeks in over 70% of cases. It is therefore important to clarify to the parents who choose to have ER that most of the excess loss with ER occurs several weeks after the procedure and is likely to be the consequence of the resorbing dead fetoplacental tissue, rather than the technique itself.

The increased risk of miscarriage after ER is offset by a decrease in early preterm birth from about 28 to 10%, so that

![Figure 2. Frequency distribution showing the gestation at delivery of triplet pregnancies managed expectantly (open histograms) and those with embryo reduction (ER) to twins (black histograms).](https://academic.oup.com/humrep/article-abstract/21/7/1912/2938488)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Gestation (weeks)</th>
<th>(N)</th>
<th>Miscarriage &lt;24 weeks</th>
<th>Delivery at 24–31 weeks</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porreco et al. (1991)</td>
<td>10–11</td>
<td>24</td>
<td>0/11 (0.0)</td>
<td>1/13 (7.7)</td>
<td>Difference in gestational age at recruitment between expectant and reduction groups (9 and 9–15 weeks respectively)</td>
</tr>
<tr>
<td>Bollen et al. (1993)</td>
<td>7</td>
<td>72</td>
<td>2/39 (5.1)</td>
<td>3/33 (9.1)</td>
<td>Difference in gestational age at recruitment between expectant and reduction groups (9 and 11–13 weeks respectively)</td>
</tr>
<tr>
<td>Check et al. (1993)</td>
<td>9–13</td>
<td>29</td>
<td>0/23 (0.0)</td>
<td>0/6 (0.0)</td>
<td>No data on gestational age at ER</td>
</tr>
<tr>
<td>Boulot et al. (2000)</td>
<td>8–13</td>
<td>148</td>
<td>5/83 (6.0)</td>
<td>5/65 (7.7)</td>
<td>Data included in a subsequent study (Boulot et al., 2000)</td>
</tr>
<tr>
<td>Antsaklis et al. (2004)</td>
<td>8–14</td>
<td>255</td>
<td>2/70 (2.9)</td>
<td>15/185 (8.1)</td>
<td>Data included in current study</td>
</tr>
<tr>
<td>Current study</td>
<td>10–14</td>
<td>365</td>
<td>9/185 (4.9)</td>
<td>15/180 (8.3)</td>
<td>Data included in current study</td>
</tr>
<tr>
<td>Total</td>
<td>10–14</td>
<td>365</td>
<td>18/411 (4.4)</td>
<td>39/482 (8.1)</td>
<td>Not possible to calculate the numbers of miscarriages and early preterm deliveries</td>
</tr>
<tr>
<td>Total trichorionic</td>
<td>10–14</td>
<td>365</td>
<td>11/255 (4.3)</td>
<td>30/365 (8.2)</td>
<td>Not possible to calculate the numbers of early preterm deliveries</td>
</tr>
</tbody>
</table>

In only two of the papers it is stated that all pregnancies were trichorionic (Antsaklis et al., 2004; current study).

*In the calculation of the rate of early delivery, the denominator is the number of pregnancies that did not miscarry before 24 weeks.*

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gestational age at delivery is significantly higher when compared to expectantly managed triplets. As the risk of neonatal death and severe handicap is primarily dependent on gestation at delivery it may be that the ER-related prolongation of gestation at delivery could decrease perinatal death and handicap among survivors. We have previously estimated that ER would reduce the handicap rate from about 1.5% in expectant management to 0.6% (Papageorghiou et al., 2002). However, in our estimates we assumed survival and handicap rates for singleton pregnancies, because of sparcity of data in the literature for such outcomes in triplets. Even less long-term information is available for infants born after ER in co-multiples, but there is some concern that periventricular leukomalacia in preterm infants, a strong predictor of cerebral palsy, is more common after ER (Geva et al., 1998).

The literature search yielded no randomized, controlled trials of ER versus expectant management in triplets. This was also true in a recent Cochrane review of ER in higher order pregnancies (Dodd and Crowther, 2003). A randomized trial of the two management options in triplet pregnancy would undoubtedly

Figure 3. Cochrane plots (random effects model) for miscarriage (top) and early preterm birth (bottom) in triplet pregnancies, following embryo reduction (ER) versus expectant management.
allow a clearer picture of their relative merits. On the assumption that, as shown in our systematic review, the prevalence of early preterm delivery could be reduced by ER from 28 to 10%, a randomized study would require enrolment of over 320 pregnancies to show that such a difference is significant (90% power at the 0.05% level). Studies examining the arguably more relevant outcomes of perinatal mortality or handicap rate would be similarly impractical as the numbers required to achieve statistical significance would be even larger. In our clinical experience, parents have preferences regarding expectant management or pregnancy reduction, and we believe that it is unlikely that enough parents would be in equipoise about the management of their pregnancy in order to successfully complete such a study.

In the absence of randomized trials, clinical decisions and patient counselling on the best management of triplet pregnancies need to rely on the data from observational studies. However, it is important that such observational data are carefully scrutinized in order to avoid bias. We have limited our review to two important pregnancy outcomes, namely miscarriage and early preterm delivery, as these are widely reported in the literature, allowing combination of several studies. Furthermore, we excluded the studies in which there were differences in gestational age at recruitment between the two management groups, because the rate of spontaneous fetal loss decreases with advancing gestation. One important limitation of the meta-analysis was that only two of the six studies specified the chorionicity of their pregnancies. Certainly in monochorionic twins, the rates of miscarriage and early preterm delivery are substantially higher than in dichorionic twins (Sebire et al., 2005), multifetal pregnancy reduction following multiple embryo transfer remains a mainstay of inferential age at recruitment between the two management groups, because the rate of spontaneous fetal loss decreases with advancing gestation. One important limitation of the meta-analysis was that only two of the six studies specified the chorionicity of their pregnancies. Certainly in monochorionic twins, the rates of miscarriage and early preterm delivery are substantially higher than in dichorionic twins (Sebire et al., 1997b), and the same is likely to be true in dichorionic or monochorionic triplets, compared to trichorionic triplets. Nevertheless, since the incidence of such triplets is low (around 15%), it is unlikely that the results would have been significantly affected, and when the meta-analysis was limited to the two studies which specified chorionicity the results were similar.

Although there is evidence that there has been a halt of the inexorable rise in triplet births over the last 2–3 years (Simmons et al., 2004; Martin et al., 2005), multifetal pregnancy reduction following multiple embryo transfer remains a mainstay of infertility therapy in many centres. It is important to recognize that we have insufficient information about the long-term impact of the death of a co-multiple early in pregnancy on the well-being of survivors (Kurinczuk, 2003) and at present we believe that there are insufficient data to recommend a policy of pregnancy reduction to women with trichorionic triplet pregnancies.

On the basis of the existing data, the parents should be counselled that ER reduces the risk of early preterm delivery but at the expense of increasing the risk of miscarriage.

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References


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