The outcome of twin pregnancies after IVF

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It has been suggested that the high rates of prematurity, low birth weight, perinatal morbidity and mortality in in-vitro fertilization (IVF) infants are due to the increased frequency of multiple gestations in this population. The aim of our study was to test this hypothesis by comparing the outcome of IVF twins with that of twins born after spontaneously conceived pregnancies. The perinatal outcome of 40 IVF twins was compared with that of 80 control twins, matched for maternal age, parity and ethnic origin. IVF twins had a higher rate of prematurity ($P = 0.03$), their mean birth weight was significantly lower ($P < 0.01$) and the frequency of very low birth weight infants was much higher ($P < 0.003$). There was no neonatal mortality in the control group, whereas four IVF twins died ($P < 0.01$). Neonatal morbidity was significantly greater in IVF twins ($P < 0.05$). Oxygen therapy and mechanical ventilation were administered more frequently to IVF twins ($P < 0.007$ and $P < 0.05$). We conclude that twins conceived by IVF are at a significantly higher risk for prematurity and associated neonatal morbidity and mortality than spontaneously conceived twins.

**Key words:** IVF/neonatal morbidity/prematurity/twins

**Introduction**

In-vitro fertilization (IVF) pregnancies have been associated with relatively high rates of fetal loss and ectopic pregnancies as well as high rates of prematurity, low birth weight and perinatal complications (Australian IVF Collaborative Group, 1985; Beral et al., 1990; MRC Working Party, 1990; Schenker and Ezra, 1994). In order to increase the rate of success of the procedure, several embryos are typically transferred, resulting in a high rate of multiple gestation (15–30%). Multiple gestation is associated with prematurity, low birth weight and increased perinatal morbidity and mortality (Botting et al., 1987; Luke and Keith, 1992).

Therefore it has been suggested that the increased rates of prematurity, low birth weight, perinatal morbidity and mortality amongst infants born by IVF may be attributed to the increased number of multiple gestations in this population (Beral et al., 1990; MRC Working Party, 1990). Furthermore, Tallo et al. (1995) have recently published data indicating that multiple gestations account for most of the neonatal morbidity amongst IVF babies.

The objective of this study was to test the aforementioned hypothesis by comparing the perinatal outcome of IVF twins with that of twins born as a result of spontaneous conception.

**Materials and methods**

This case-control study was conducted at Bikur Cholim Hospital, a university-affiliated hospital with comprehensive tertiary perinatal care facilities. The study sample included all IVF twins born in the hospital from January 1990 until July 1995. There were 20 IVF twin deliveries, i.e. 40 babies. Each IVF mother was matched to two control mothers by age ($\pm 3$ years), parity and ethnic origin. The control group included 40 pairs of spontaneous twins, i.e. 80 babies. In both groups, all pairs of twins were dizygotic.

For IVF pregnancies, the length of gestation was calculated by adding 14 days to the interval between the dates of fertilization and birth. The gestational age of control infants was calculated as the difference between the date of the last menstrual period and the date of birth concordant with neonatal examination – either the Dubowitz score, or in premature infants younger than 34 weeks, by examination of blood vessels in the anterior capsule of the lens. Prematurity was defined as delivery prior to 37 weeks gestation. Low birth weight (LBW) was defined as $<$2500 g and very low birth weight (VLBW) as $<$1500 g. Infants were classified by birth weight as appropriate, small or large for gestational age on the basis of the Colorado intrauterine growth charts. The term morbidity included all the major illnesses of the neonate: respiratory distress syndrome, transient tachypnoea of the newborn, sepsis (by clinical presentation and positive blood culture), necrotizing enterocolitis (by clinical presentation and radiographic studies) and intraventricular haemorrhage (by ultrasound examination). Any infant who suffered from one or more of the above illnesses was considered to have suffered serious morbidity.

The following parameters were compared: gestational age at delivery, rate of premature deliveries, type of delivery (vaginal versus Caesarean delivery), birth weights, prevalence of LBW and VLBW infants, appropriateness of weight for gestational age, Apgar scores, length of hospitalization, and admissions to the neonatal intensive care unit (NICU). We also compared neonatal mortality, morbidity, administration of antibiotics, oxygen therapy and mechanical ventilation.

All information was gathered from patients’ hospital records. Statistical methods included $t$-tests for continuous variables and Fisher exact tests for discrete variables. Subsequently, multivariate analysis was applied using a proportional odds logistic model for ordered variables to annul the effect of twinning. The order of the dependent variable (e.g. morbidity) was determined by twinning: if neither twin was affected; 1: if one of the twins was affected; 2: if both twins were affected. The proportional odds logistic regression was also used to adjust for the effect of confounding variables such as maternal age and parity.
Table I. Birth characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IVF (total = 40)</th>
<th>Control (total = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>36 (4)</td>
<td>37 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Prematurity n (%) (&lt;37 weeks)</td>
<td>24 (60)</td>
<td>16 (40)</td>
<td>0.03</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2074 ± 590</td>
<td>2361 ± 468</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Range</td>
<td>690–3050</td>
<td>1150–3520</td>
<td></td>
</tr>
<tr>
<td>LBW (1501–2500 g) n (%)</td>
<td>18 (45)</td>
<td>44 (55)</td>
<td></td>
</tr>
<tr>
<td>VLBW (&lt;1500 g) n (%)</td>
<td>10 (25)</td>
<td>3 (4)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>AGA n (%)</td>
<td>28 (70)</td>
<td>65 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>SGA n (%)</td>
<td>12 (30)</td>
<td>15 (19)</td>
<td>NS</td>
</tr>
</tbody>
</table>

aValues are means ± SD, unless otherwise indicated.
bValues are medians (interquartile range).

LBW = low birth weight; VLBW = very low birth weight; AGA = appropriate for gestational age; SGA = small for gestational age.

Results

The mothers were perfectly matched for parity and ethnic origin. The mean ± SD age of IVF mothers was 30.9 ± 4.2 years, compared to 29.3 ± 4.1 years in the control group (non-significant).

In all, 65% (13/20) of IVF deliveries were by Caesarean section, compared to 53% (21/40) in the control group. The difference was not statistically significant. Examination of obstetric records showed that almost all of the Caesarean sections in the IVF group (10/13) were performed after the early onset of labour and the indication for surgery was malpresentation. Only one operation was performed electively at 36 weeks gestation. Two operations were indicated by fetal distress, one at 34 weeks and the other at 40 weeks.

Table I shows birth characteristics. The gestational age at delivery tended to be lower in the IVF group, and the rate of premature deliveries was significantly higher (P = 0.03). The average birth weight of IVF twins was markedly lower than their controls (P < 0.01). Amongst the IVF babies, 25% (10/40) were VLBW, compared to only 4% (3/80) in the control group (P < 0.003). We found no significant difference in Apgar scores, either at 1 min or at 5 min of age.

The average length of hospitalization for IVF twins was 11.5 ± 14.2 days, and for control twins 12.3 ± 10.8 days. A total of 40% (16/40) of IVF babies were admitted to the NICU, compared to 29% (23/80) of controls. Neither the increased length of hospitalization nor the greater rate of intensive care admissions of the IVF babies was statistically significant.

Table II compares neonatal outcome. In the control group, all 80 twins survived. In the IVF group, four babies (one pair of twins and two unrelated babies) died in the neonatal period, i.e. 10% mortality (P < 0.01). The twins who died were extremely premature, VLBW babies: twin A died of persistent pulmonary hypertension, while twin B suffered from severe respiratory distress syndrome, pneumothorax and massive intraventricular haemorrhage. Of the two unrelated infants, one was born at 36 weeks with anencephalus. The other was a premature infant (33 weeks, weighing 1300 g) who succumbed to perforated necrotizing enterocolitis.

Morbidity was significantly greater in the IVF group than in the control group: 25% (10/40) versus 9% (7/80) (P < 0.05).

Proportional odds logistic regression demonstrated that prematurity and low birth weight were the main determinants of increased morbidity. The odds ratio for the morbidity of premature infants versus term infants was 4.6 with a 95% confidence interval (range 1.11–19.2).

Discussion

In a recently published study, Peterson et al. (1995) found no significant difference in gestational age between IVF babies and controls. In singleton deliveries they found a lower birth weight in the IVF group, whereas in multiple gestations similar birth weights were found in the IVF and control groups. Lipitz et al. (1993) published data comparing triplets conceived after IVF and fertility drugs with spontaneous triplets. They found no difference in gestational age, birth weight or morbidity between the three groups. However, it should be noted that in all three groups the vast majority of the triplets were born prematurely (on average at or around 34 weeks of gestation) and the frequency of LBW infants was >90%. Oliviennes et al. (1996) found no difference in the global rate of prematurity in their comparison of twin pregnancies obtained after IVF with those obtained spontaneously or after ovarian stimulation. However they did find that very premature deliveries (prior to 31 weeks of gestation) were more frequent in the IVF group. It should be noted that their study excluded deliveries prior to 28 weeks of gestation. Had deliveries between 24 and 28 weeks gestation been included, it is possible that this finding would have been even more significant.

Our data show an increased tendency to lower gestational age in IVF twins. Data published by the MRC Working Party on children conceived by IVF (1990) showed that in Great Britain, 24% of IVF pregnancies ended before 37 weeks compared to only 6% in the general population. It has also been reported that 50% of twin pregnancies end before 37 weeks (Ghai and Vidyasager, 1988). We found that 60% of IVF twins were born prematurely, compared to only 40% of the control twins. Our findings are similar to those reported by Tallo et al. (1995).
We found that the mean birth weight of the IVF twins was significantly lower than that of their controls. In general, >50% of twins weigh <2500 g at birth, more than six times the rate of LBW in singletons (Ghai and Vidyasager, 1988). In our study, almost 60% of the control twins were LBW, as were 70% of the IVF twins. When the LBW infants were further divided into LBW and VLBW categories, the difference between the two groups was marked. Of the IVF twins, 25% weighed <1500 g, six times the rate in the control group. The statistical significance of this finding is surpassed only by the clinical implications of such a large, high risk population. We did not find any difference in appropriateness for gestational age; thus the lower birth weights of the IVF twins were a result of the higher rate of prematurity.

The differences in neonatal morbidity and mortality were particularly striking. In the control group there were no neonatal deaths, whereas four out of 40 IVF twins died in the neonatal period. Morbidity among the IVF twins was almost three times that of the controls. Tallo et al. (1995) also reported significantly higher incidence of respiratory distress system treated with surfactant, patent ductus arteriosus treated with indomethacin, and culture proven sepsis amongst IVF twins when compared to non-IVF controls.

In the control group, only two neonates required mechanical ventilation and oxygen therapy. Obviously as a consequence of the increased rate of serious morbidity, 15% of IVF twins required mechanical ventilation, and 23% needed oxygen therapy. The statistical and clinical significance of these differences is clear.

Multivariate analysis indicated that the poorer neonatal outcome in the IVF group was a result of the higher percentage of premature, (very) low birth weight infants.

We thus conclude that IVF twins have a poorer neonatal prognosis than their counterparts born after normal spontaneous twin pregnancies, mainly due to a higher rate of prematurity.

Many studies have noted a high frequency of prematurity amongst babies born by IVF. Beral et al. (1990) attributed this in part to the high proportion of multiple births but noted that IVF singletons are also delivered earlier than their spontaneous counterparts. They could not identify a clear cause of this increased frequency of prematurity. It has been suggested that IVF pregnancies are more closely monitored than other pregnancies and as such are subject to more obstetric intervention, i.e. induction of labour and Caesarean sections (Australian IVF Collaborative Group, 1985). The MRC working party (1990) concluded that increased prematurity was not due to induction of labour. In our study we did observe an increased rate of Caesarean sections in the IVF group, but this difference was not statistically significant. In the study group, one premature delivery was due to fetal distress, another was due to pre-eclamptic toxemia and all other premature deliveries were babies born to mothers who were admitted with spontaneous early onset of delivery. We were unable to identify any specific maternal risk factor for the early onset of labour.

Grouetz et al. (1996) have also recently reported a higher incidence of pregnancy complications after multifetal pregnancy reduction to twins, compared with spontaneous twins; these complications included premature contractions and pregnancy-induced hypertension.

In contrast to the widely held opinion that multiple gestation is the main cause of increased morbidity in IVF, our findings suggest that IVF is an important independent risk factor for prematurity, low birth weight and the resultant morbidity. The cause or causes of this increased tendency to prematurity remain unclear, and are worthy of further investigation. It is interesting that Wennerholm et al. (1996) found a lower incidence of multiple births, preterm deliveries, low birth weights and congenital malformations in infants born after intracytoplasmic sperm injection (ICSI) compared to IVF pregnancies not associated with ICSI.

Unlike the studies by Lipitz et al. (1993) and Oliiviennes et al. (1996), which compared the outcome of conceptions obtained after IVF with that of conceptions obtained after ovarian stimulation, as well as with that of spontaneous conceptions, our study did not include a cohort of twins conceived after ovarian stimulation followed by natural intercourse. Therefore we cannot address the important question of whether the observed tendency to prematurity is a result of ovarian stimulation or IVF per se. This too must be a subject for further investigation.

In conclusion, we feel that IVF babies tend to be born earlier than their spontaneous peers. When triplets are studied (as in the study by Lipitz et al., 1993), the clinical significance of this tendency to earlier delivery is reduced, since most triplets are born prematurely. Conversely, when IVF singletons are studied, any tendency to lower gestational age (e.g. 37–38 weeks rather than 39–40 weeks) also has no great clinical impact. However in the case of IVF twins, we suggest that this tendency to prematurity is of great clinical significance. It must not be forgotten that all twin gestations are high risk pregnancies and deliveries. IVF twins are in ‘double jeopardy’. Not only are they twins, but they are also likely to be delivered earlier than spontaneous twins and to suffer from the morbidity associated with prematurity and low birth weight. Clearly, this must be considered when deciding how many fertilized ova to re-implant, or when making decisions regarding fetal reduction.

References


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