OPINION

Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies?

M.van Wely¹,3, M.Twisk¹, B.W.Mol¹,2 and F.van der Veen¹

¹Center for Reproductive Medicine, Academic Medical Center, Amsterdam and ²Department of Obstetrics and Gynaecology, Máxima Medical Center, Veldhoven, The Netherlands

³To whom correspondence should be addressed at: Center for Reproductive Medicine, Academic Medical Center, Meibergdreef 9, H4-213, 1105 AZ Amsterdam, The Netherlands. E-mail: m.vanwely@amc.uva.nl

It has recently been suggested that the measure of success of assisted reproductive technologies (ART) should be the birth of a singleton baby, whereas a twin pregnancy should be considered as a complication. Although the maternal and neonatal complications in twin pregnancies are significantly higher than those in singleton pregnancies, the classification of a twin pregnancy as a complication of ART is in our opinion debatable. Most twin pregnancies result in the birth of two healthy babies, with little or no complication for the mother, and only few twin pregnancies result in serious morbidity of the mother and of one or both of the children. The crux of our arguments is that one should consider those cases as poor outcomes and not a twin pregnancy per se.

Key words: artificial reproductive technologies (ART)/complications/twin pregnancy

Twin pregnancies after assisted reproductive technologies

At present, more than half of all twin pregnancies are the result of assisted reproductive technologies (ART). The twin pregnancy rate after intrauterine insemination (IUI) is about 10% (Andersen et al., 2005; Steures et al., 2006), whereas after IVF/ICSI, the twin pregnancy rate often is ∼25% (Andersen et al., 2005). As twin pregnancies are associated with medical complications, more and more gynaecologists consider twins as an adverse treatment outcome and advocate strategies with a low chance of multiple pregnancy. This has resulted in a change in the desired outcome of ART. Whereas in the past, the birth of a singleton or a twin was considered a success, this view has changed in recent years. At the European Society of Human Reproduction and Embryology (ESHRE) consensus meeting in 2002, it was agreed that the preferred outcome of ART should be the birth of one healthy child and that a twin pregnancy should be considered as a complication (Land and Evers, 2003).

Twin pregnancies after IUI arise mainly when ovarian stimulation is used. Banning stimulation from all IUI cycles would prevent most twin pregnancies but would result in a lower pregnancy rate. In couples with unexplained subfertility, meta-analyses have shown that IUI in a stimulated cycle with gonadotrophins results in more pregnancies than IUI in a natural cycle [odds ratio 2.0; 95% confidence interval (CI) 1.4–2.8] (Hughes, 1997; Cohlen, 2005).

In IVF and ICSI, twin pregnancies can be prevented by using elective single embryo transfer (eSET) instead of double embryo transfer (DET). However, this policy would reduce the total number of couples in whom the wish for a child is fulfilled (Pandian et al., 2005). To improve pregnancy rates after eSET, we can add transfer of a frozen and thawed embryo or offer extra cycles with eSET (Thurin et al., 2004; Lukassen et al., 2005; Pinborg et al., 2005). However, cryopreservation cycles can be offered after DET as well, and the number of IVF-eSET cycles needed to obtain pregnancy rates comparable with three cycles of DET is yet unknown.

In this contribution to the debate, we question whether a twin pregnancy is necessarily an adverse outcome of ART.

Medical complications of a twin pregnancy

Twin pregnancies present substantial perinatal risks to both the mother and the infants. Mothers carrying a twin pregnancy have higher rates of ante- and post-partum complications, like pre-eclampsia [12.5 versus 3.4%, relative risk (RR) 3.7, 95% CI 3.3–4.3), eclampsia (0.2 versus 0.1%, RR 3.4, 95% CI 1.2–9.4), placental abruption (0.9 versus 0.5%, RR 2.0, 95% CI 1.2–3.3), post-partum haemorrhage (3.1 versus 0.9%, RR 3.4, 95% CI 2.9–4.1) and anaemia (27.5 versus 16.2%, RR 1.7, 95% CI 1.5–1.9) (ESHRE Capri Workshop Group, 2000; Campbell and Templeton, 2004), than women with singleton pregnancies . Twin pregnancies also result more often in a Caesarean section (Pinborg et al., 2004a).

For the infant, the most important risk of a twin pregnancy is preterm birth (Table I). The most common complications in prematurely delivered children are respiratory...
ideal number of children is two (Stobel-Richter et al., 2005). Some couples, especially those of advanced maternal age or with fertility problems, may consider a twin pregnancy as their only chance of achieving this.

We are aware of eight studies that evaluated the preference for a singleton or a twin in infertile women undergoing a fertility treatment (Gleicher et al., 1995; Grobman et al., 2001; Kalra et al., 2003; Pinborg et al., 2003; Child et al., 2004; Murray et al., 2004; Ryan et al., 2004; Steures et al., 2005). Obviously, these studies differed in design and in the way preferences for a singleton or twin were assessed. The preferences of the patients varied strongly between studies and were likely to depend on the way the question was asked. Despite their differences, all these studies showed that a significant proportion of women had a clear preference for a twin pregnancy (Table II). Long duration of infertility, previous infertility treatments, nulliparity, age of the woman and perception of increased fetal or maternal risks were determinants for a twin preference (Gleicher et al., 1995; Grobman et al., 2001; Child et al., 2004; Ryan et al., 2004).

The largest preference study actually evaluated the preference for a twin or singleton pregnancy of mothers of IVF/ICSI twins (266), IVF/ICSI singletons (764) and mothers of spontaneous twins (739) (Pinborg et al., 2003). Mothers were approached with questionnaires at the time their children were 3–4 years of age and were asked whether they found either a singleton or twins most desirable as their first pregnancy. The study showed that 85% of IVF/ICSI-twin mothers and 62% of IVF/ICSI-singleton mothers would have preferred twins as their

### Table I. Perinatal outcome in twins and singletons after IVF/ICSI (from Pinborg et al., 2004b)

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Twins (n = 3438)</th>
<th>Singletons (n = 5164)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2500</td>
<td>42%</td>
<td>5.9%</td>
<td>7.1 (6.3–8.0)</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>7.5%</td>
<td>1.5%</td>
<td>5.0 (3.9–6.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2508 (615)</td>
<td>3457 (629)</td>
<td>–</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32–37</td>
<td>35.4%</td>
<td>6.0%</td>
<td>5.9 (5.2–6.6)</td>
</tr>
<tr>
<td>&lt;32</td>
<td>8.5%</td>
<td>1.3%</td>
<td>6.5 (5.0–8.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>35.9 (3.0)</td>
<td>39.3 (2.2)</td>
<td>–</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillborn</td>
<td>45 (1.3%)</td>
<td>34 (0.66%)</td>
<td>1.4 (1.2–1.7)</td>
</tr>
<tr>
<td>Neonatal death within 7 days</td>
<td>26 (0.76%)</td>
<td>23 (0.45%)</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>Neonatal death within 1 year</td>
<td>35 (1.0%)</td>
<td>37 (0.72%)</td>
<td>1.2 (0.96–1.6)</td>
</tr>
<tr>
<td>Birth defects per child born</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major defect</td>
<td>137 (4.0%)</td>
<td>189 (3.7%)</td>
<td>1.1 (0.9–1.2)</td>
</tr>
<tr>
<td>Minor defects without patent ductus arteriosus</td>
<td>55 (1.6%)</td>
<td>75 (1.5%)</td>
<td>1.1 (0.8–1.6)</td>
</tr>
<tr>
<td>patent ductus arteriosus</td>
<td>58 (1.7%)</td>
<td>18 (0.3%)</td>
<td>4.8 (2.6–8.2)</td>
</tr>
<tr>
<td>Total without patent ductus arteriosus</td>
<td>192 (5.7%)</td>
<td>264 (5.1%)</td>
<td>1.1 (0.9–1.3)</td>
</tr>
</tbody>
</table>

### Table II. Preference for a twin pregnancy in infertile women

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Preference for twin pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleicher</td>
<td>1995</td>
<td>582</td>
<td>67–90</td>
</tr>
<tr>
<td>Grobman</td>
<td>2001</td>
<td>200</td>
<td>67</td>
</tr>
<tr>
<td>Pinborg</td>
<td>2003</td>
<td>1030</td>
<td>62–85</td>
</tr>
<tr>
<td>Kalra</td>
<td>2003</td>
<td>180</td>
<td>30–38</td>
</tr>
<tr>
<td>Ryan</td>
<td>2004</td>
<td>449</td>
<td>20</td>
</tr>
<tr>
<td>Child</td>
<td>2004</td>
<td>801</td>
<td>41</td>
</tr>
<tr>
<td>Murray</td>
<td>2004</td>
<td>200</td>
<td>40</td>
</tr>
<tr>
<td>Steures</td>
<td>2005</td>
<td>40</td>
<td>77</td>
</tr>
</tbody>
</table>

distress syndrome, bronchopulmonary dysplasia, intraventricular bleeding, cerebral palsy and pneumonia. Apart from prematurity, twin pregnancies have an increased risk of growth retardation compared with singleton pregnancies after IVF, and almost half of all children from a twin pregnancy have a birthweight below 2500 g (ESHRE Capri Workshop Group, 2000; Pinborg et al., 2004b).

An important concern in twin pregnancies is the risk of neurological sequelae, defined as cerebral palsy, mental retardation, severe mental developmental disturbances and retarded psychomotor development. Indeed, in population-based studies on naturally conceived children, twins had four times the risk of cerebral palsy as that of singletons (Scher et al., 2002). However, in a large cohort study, it was shown that singletons from assisted conception have a similar increased risk of neurological sequelae as that of naturally conceived twins and twins from assisted conception (Pinborg et al., 2004c). Apparently, the increased risk of cerebral palsy and other neurological sequelae in natural and IVF twins is also seen in singleton pregnancies after IVF.

Because of improved perinatal care, the maternal and perinatal risks of twin pregnancies have decreased. The survival rate for twins until one year after birth is 976.7/1000 children (Pinborg et al., 2004b). For singletons, this rate is 986.3/1000 children. As reports on long-term neonatal outcome are lacking on the different types of abnormalities rather than on healthy children, the number of children that survive without handicaps is not known. However, 9 of 10 children are born after 32 completed weeks, and the prognosis for these children is usually good (Pinborg et al., 2004b).

In conclusion, although multiple pregnancies are associated with an increased risk of complications for mother and child, these complications occur only in few twin pregnancies as most pregnancies result in the birth of two healthy children.

### How do the infertile couples value singletons and twins?

In the valuation of twins, not only are medical outcomes relevant but also is the opinion of couples who have an unfulfilled wish for a child. For most couples who desire to conceive, the
first delivery outcome compared with 60% of the non-IVF/ICSI-twin mothers.

There is a difference in the perception of the desirability of twin pregnancy between medical specialists and subfertile couples (Hartshorne and Lilford, 2002). Medical specialists often wonder whether fertility patients are aware of the practical, financial and emotional consequences of the birth of a twin. According to one study, a large proportion of women that visit the clinic for the first time are already familiar with the risks of twins (Ryan et al., 2004). In this survey, almost all women were aware of the risk for prematurity, whereas 80% was aware of the increased risk for maternal morbidity and 30% about the increased neonatal mortality risk.

It has also been studied how couples who underwent a fertility treatment estimated their chances for complications following a twin pregnancy (Kalra et al., 2003). Women estimated the incidence of prematurity, low birthweight, pre-eclampsia and post-partum depression slightly higher than their partner (27 versus 17%, 26 versus 17%, 22 versus 16% and 21 versus 16%, respectively). Despite these high estimations of complications, there was a general preference for twins over singleton in both sexes.

In conclusion, subfertile couples or mothers of twins value a twin in general more than a singleton pregnancy.

Consequences for future research and clinical practice
At present, the multiple pregnancy rate after ART is high, and efforts to reduce this should be carefully considered. In our opinion, a balance should be struck between the complications of multiple pregnancies and the overall number of couples whose wish for a child is fulfilled. It is obvious that twin pregnancies can be prevented after ART treatment: in IUI by not using ovarian stimulation and in IVF/ICSI by using an eSET policy. However, the question should be whether the overall drop in pregnancy rate is justified by the reduction in multiple pregnancies. To address this issue carefully, it is necessary to consider not only the multiple pregnancy per se but also the neonatal mortality and morbidity associated with various strategies.

Conclusions
We are not promoting the creation of twins here. The medical risks of twin pregnancies should not be underestimated. The reaction of opinion leaders in the field on the issue of multiple pregnancies however has been remarkable. Controlled ovarian hyperstimulation in IUI programmes has been banned in many centres without an attempt to provide proper evidence. Furthermore, in IVF programmes, eSET is being pushed forward in several countries now, based upon limited evidence. In our view, it is equally important to take the preferences of the couples themselves into account. Subfertile couples appear to accept the risk of a twin pregnancy, and as we have shown in this debate, these couples generally do not consider a twin pregnancy as problematic. Considering all arguments, we feel that a twin pregnancy that results in the birth of two healthy children does not necessarily deserve to be condemned as an adverse outcome.

References