ART and major structural birth defects in the United States

Sir,

We read with interest the study by Reefhuis et al. (2009) showing that assisted reproductive technology (ART) treatment is a risk for structural birth defects. The authors recognize that this risk may be over-stated because underlying subfertility may in itself be an important risk factor for such defects. In our meta-analysis of 19 studies (Rimm et al., 2004), where we found an overall risk of 1.29, we noted the failure of each of those 19 studies to use the most appropriate control group, namely infertile couples conceiving spontaneously.

Responding to the concern we raised, Zhu et al. (2006) attempted to design an analysis with a control group made up of subfertile couples. They compared three groups of children: those born of fertile couples (Group A), those born of infertile couples who conceived spontaneously after 12 months (Group B) and those born of infertile couples who conceived after ART treatment (Group C). They found that when compared with Group A, singletons in Group B and in Group C both had a higher incidence of congenital malformations. The adjusted hazard ratios were 1.20 [95% confidence interval (CI): 1.07–1.33] and 1.39, respectively (95% CI: 1.23–1.57). When the singletons in Group C were compared with those in Group B, the adjusted hazard ratio was 1.17 (95% CI: 1.00–1.36). Zhu et al. suggested that some of the determinants of infertility might share a common causal pathway with mechanisms that cause congenital malformations.

We were surprised that the Reefhuis study presents no overall rate of malformations in women aged 35 and over. Apparently there is a very large difference in the age distribution of the ART group and the non-ART group as shown in Table 1 for those without major birth defects. Only 13% of the non-ART mothers were 35 and older, whereas 55% of the ART mothers were 35 or older. The authors failed to show the age of the ART and non-ART mothers with a major defect. When there is such a large difference in the age distribution between the two groups, adjustment for age is not a sensitive method of analysis. Stratifying by age is more sensitive because it takes interaction into account.

We also note that this report does not present an overall odds ratio combining the 25 defect categories that were studied. It would be interesting to know whether that odds ratio was statistically significant.

In this type of study where apparently there is no overall significant risk, the authors proceeded to make 25 individual comparisons, one for each defect. Apparently there was no adjustment for multiple comparisons. If they had made the adjustment, the p-values would have to be 0.002 or less for significance at the 5% level. It appears that if the adjustment were made, none of the four individual defects found significant would truly be statistically significant at the 5% level.

In the ART-treated group, Zhu observed an increasing incidence of congenital malformations with increasing time to pregnancy (TTP) when comparing 6–12 months TTP with ≥12 months TTP. This would suggest that successful treatment interrupts or cuts short the period when a subfertile couple can conceive spontaneously, and may offer some protection against delay, which apparently increases risk. Furthermore, if TTP is longer, the patient will be older when conception occurs. Shortening TTP may reduce the patient’s age at the time of conception.

The Reefhuis study, like all before it, lacks a control group made up of subfertile couples. As a result, this study may not only overstate the risk, but it may also obscure the possible fact that ART actually protects against defects. For example, a protective effect may arise in the ART clinic laboratory where a variety of selection processes occur, ranging from PGD to the objective and subjective ways in which the embryologist selects gametes and embryos.

Until more studies are designed using subfertile couples conceiving spontaneously as the control group and until more data on the relationship between TTP and age and congenital malformations are known, it is premature to state that ART itself increases the risk of malformations.

References


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