Adverse Effects of Assisted Reproductive Technology and Pregnancy Outcome

A review of: Stromberg B, Dahlquist LG, Ericson A *et al*. 2002 Teratological sequelae in children born after in vitro fertilization: A population based study. Lancet 359: 461–465; Schieve LA, Meikle SF, Ferre C *et al*. 2002 Low and very low birth weight in infants conceived with use of assisted reproductive technology. N Engl J Med 346:731–737; and Hansen M, Kurnczuk JJ, Bower C, *et al*. 2002 The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. N Engl J Med 346:725–730

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In vitro fertilization (IVF) is undoubtedly one of the most important achievements of medical science in the last generation. Similar to other revolutionary modalities, serious adverse effects of new methodologies take years to surface, because most significant side effects are rare. The question of whether manipulation of the human egg and sperm will cause them damage has always been of high priority for biologists and clinicians advancing the field of IVF. Until recently, emphasis has been focused on increasing the efficiency of the process, while decreasing the morbidity associated with multiple pregnancies.

In February 2002, a group from Uppsala, Sweden, reported a retrospective cohort study linking and comparing neurological disorders among 5,680 infants born after IVF with 11,360 matched controls (1). The cohort included 2,060 twins born after IVF who were matched with 4,120 twins as controls. Data on neurological morbidity was obtained from the records of the habilitation centers caring for these children.

In general, children born following IVF were more likely to require the services of a habilitation center than controls, and the odds ratio (OR) for cerebral palsy (CP), the most common form of neurological morbidity, was 3.7 (95%CI: 2–6.6). These abnormalities were largely due to the high frequency of twin pregnancy, low birth weight, and prematurity. However, multivariate analysis revealed that IVF independently contributed to the risk of CP. Most of the difference was among singletons, whereas twins born after IVP did not differ from matched control twins for neurological risk. It is puzzling that the risk for neurological damage was significant among singletons. In an editorial comment, Healy and Saunders note that the rates of CP were lower than expected among the controls (2). If these results are biologically true, they may represent an adverse biological effect of IVF on motor development. Alternatively, it is possible that infertility itself contributes in a yet unknown way to the pathophysiology of CP.

In March 2002, two studies in the *New England Journal of Medicine* raised concerns about malformations and intrauterine growth retardation associated with the new reproductive technologies (3, 4). In a study from Australia, 26 of 301 (8.6%) infants conceived by intracytoplasmic sperm injection and 75 of 837 (8.9%) infants conceived by IVF had major birth defects, two-fold greater than controls. Following adjustments for different cofounders, the OR remained significant for each of the two techniques (5).

Because parents and health professionals closely watch for malformations in their offspring following assisted reproductive technology, the authors attempted to control for the likelihood that these infants are more likely to be identified. They assigned a blinded pediatrician to review the list of all birth defects and to identify defects that might have been diagnosed because of closer surveillance and might not otherwise have been detected in a child less than one year of age. The authors reported that the differences remained significant after removal of cases by the blinded pediatrician. Unfortunately, the author's did not provide a list of the specific malformations. However, it is evident that the children conceived by reproductive technology had, for example, significantly more cardiovascular malformations. It is more likely that children conceived by reproductive technology were tested for ventricular septal defect (VSD) whenever a murmur was identified by auscultation. Yet, the blinded reviewer did not identify VSD as a potential "surveillance bias." The same holds true for chromosomal defects, which are more likely to be sought in "precious" pregnancies as compared to healthy, normal pregnancies.

It is of interest that neither the three papers, nor the two commentaries (1–5) relate these findings back to the realm of biological plausibility, and to potential insights into mechanisms. What is it in these reproductive technologies that can disrupt the genome in a non-fatal manner, but with effects on specific organs and possibly brain development?

This does not detract from the potential importance of these new findings. However they demonstrate the need for close cooperation between medical and scientific disciplines in the development of these techniques and in the evaluation of these current findings.

1. Stromberg B, Dahlquist LG, Ericson A, Finnstrom O, Koster M, Stjernquist K 2002 Teralogical sequelae in children born after in vitro fertilization: A population based study. Lancet 359:461–465
2. Healy D, Saunders K. 2002 Follow-up of children born after in vitro fertilization. Lancet 359:459–460
3. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. 2002. Low and very low birth weight in infants conceived with use of assisted reproductive technology. N Engl J Med 346:731–737
4. Hansen M, Kurinczuk JJ, Bower C, Webb S 2002 The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. N Engl J Med 346:725–730
5. Mitchell AA. 2002 Infertility treatment: More risks and challenges. N Engl J Med 346: 769–770

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