EDITORIAL

The children of assisted reproduction—the need for an ongoing debate

Throughout the short history of assisted reproduction there has been concern to monitor the safety of this important technology. There are several components to the short- and long-term safety of treatment for the woman involved (Barlow, 1999), but perhaps the greatest challenge has been to identify whether the offspring of assisted reproduction are at greater risk of, or enter life with a greater burden of, abnormalities than their naturally-conceived peers.

In the late 1980s reports from a number of countries provided a reasonably, but not totally, reassuring picture, particularly in relation to rates of neonatal problems and congenital anomaly in registries of IVF children (Lancaster, 1987; Cohen et al., 1988; Beral and Doyle, 1990; Olivennes et al., 1993). These studies inevitably use observational methodologies that are subject to the difficulties commonly encountered in epidemiological research such as the selection of control groups and surveillance bias. Other confounding factors specific to the field which may influence outcome but which affect the IVF group but not controls include: (i) the basic infertility problem; (ii) the increased age of IVF mothers; (iii) the increased multiple pregnancy rate with IVF; (iv) the possible use of fetal reduction; (v) the direct effect of fertility drugs; (vi) the effects of IVF culture media and conditions for early cell divisions; and (vii) the effects of invasive prenatal diagnosis procedures which may be more common in the IVF group.

The case for the monitoring of the health of children conceived by assisted reproduction became even stronger with the development of invasive fertilization techniques, predominantly ICSI, and the subsequent evolution in the 1990s of invasive sperm retrieval methods to obtain epididymal or testicular sperm. Unfortunately these additional techniques increase the confounding factors, such as paternal genetic anomalies, that may affect these observational studies. Follow-up studies in this era have been emerging, particularly in a series of reports from the Brussels group (Bonduelle et al., 1998; for example). This group has recently published further generally reassuring data on ICSI (Bonduelle et al., 2002) but there has been a recent focus of attention on this matter as a result of a cluster of publications which suggests that a variety of problems over control rates are increased in different categories of IVF or ICSI cases [low birthweight (Schieve et al., 2002); major congenital anomalies (Hansen et al., 2002); sex chromosome abnormalities (Bonduelle et al., 2002); imprinting disorders (Olivennes et al., 2001); and cerebral palsy (Strömberg et al., 2002)]. This issue of Human Reproduction includes another such paper (Koivurova et al., 2002). All these reports are open to discussion over the many confounding issues and some have attracted headlines in the public media.

With the increasing complexity of the available effective assisted reproduction interventions and the growing understanding of genetic mechanisms, it is timely that those in the field reflect on what we have learned and what we need to discover.

The population of couples having assisted reproduction has never been homogeneous, but in terms of genetic complexity the assisted reproduction population is even less homogeneous since the development of ICSI and the use of testicular non-ejaculated sperm. In considering and debating outcomes we need to take this complexity into account in assessing the effects of different aspects of assisted reproduction and to what extent any increased risk may actually be associated with specific patient subsets.

Couples having ‘standard IVF’ will potentially bring to the treatment various factors which can influence outcomes, and the IVF treatment itself may affect outcomes through drug effects, effects due to in-vitro culture and effects of embryo transfer on the uterus. In some cases there may be additional procedures such as assisted hatching, embryo biopsy or embryo freezing. In considering additional complications relating to ICSI we should differentiate between mild and more severe male infertility cases. With milder cases there is less prospect for genetic problems, but there is still the theoretical potential for adverse effects via damage to the spindle, exposure to polyvinylpyrrolidone and subtle disordering of the normal processes of fertilization. With more severe male infertility there is a greater potential for passing on pre-existing paternal genetic anomalies including Y deletions or expanded trinucleotide repeats. Where surgical sperm retrieval is required this may be to overcome obstructive disorders, as with epididymal sperm retrieval, or to obtain testicular sperm. The obstructive disorders may not bring additional confounding factors, but issues such as congenital absence of the vas in cystic fibrosis (CF) should be considered as all sperm produced by such individuals will carry a CF mutation. With testicular sperm there is certainly a greater prospect for complicating factors since the sperm may be immature. The reports of rare imprinting disorders in association with the use of testicular sperm may be highlighting an issue particular to that specific technique. There also needs to be an exploration of the extent to which the risk to offspring where testicular sperm are used is simply a repeating of the father’s fertility problem and to what extent some severe male genetic problems managed by testicular sperm retrieval may increase risk of other genetic anomalies. Thus, assisted reproduction techniques applied to different patient groups may carry quite different levels of potential risk for their offspring.

Assisted reproduction has been successful for thousands of couples throughout the world and has brought much happiness to them. In doing this work there is a responsibility to have a realistic understanding of the perinatal and paediatric
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risks potentially faced by those couples. Such an understanding makes possible realistic counselling about the specific couple’s circumstances so that there can be meaningful informed consent taking into account the generalized risks of assisted reproduction and the particular issues affecting the couple. This journal has a tradition of facilitating debate and wishes to encourage debate on this complex topic. The reproductive medicine community needs to understand these complex follow-up datasets, their implications and their limitations. We have specifically invited some contributions on this topic which needs to be debated and we regard this as a long-term and continuing debate.

References


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