Children born after preimplantation genetic diagnosis show no increase in congenital anomalies

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Now over 20 years old (Handyside et al., 1990), preimplantation genetic diagnosis (PGD) is considered by some to be not only an intrinsic component of prenatal genetic diagnosis (Simpson, 2009) but more arguably a novel way to increase pregnancy rates in assisted reproductive technology (ART). PGD remains widely practiced, despite recent controversy with respect to PGD aneuploidy testing (Mastenbroek et al., 2007; Fritz, 2008). Much of this controversy concerns whether the theoretical attraction of transferring euploid embryos is subsumed by damage unavoidably occurring at embryo biopsy. Rigorous studies are similarly needed concerning abnormalities of PGD offspring. Further, the absolute frequency of abnormalities will likely be higher than in birth defects registries. Major malformations must be precisely defined and distinguished from minor anomalies.

Another problem is finding valid controls for offspring of ART and ICSI, which of course are required for PGD. The proper control group would be infertile couples who become pregnant without ART, obviously unachievable (Simpson and Liebaers, 1996; Simpson and Elias, 2003). Lacking such, it remains unclear whether any increased risk reflects the ART procedure or is due merely to underlying (heritable) reasons causing both infertility and abnormal live births. Using a similar experimental design to that employed in the current study, the authors previously reported no differences between 70 PGD, 70 ICSI offspring and 70 naturally conceived offspring (Desmyttere et al., 2009). The general consensus is that structural anomalies are increased perhaps 25–30% in ART offspring (Hansen et al., 2005). That subfertile couples (those taking >12 months to achieve pregnancy) also have anomaly rates increased over background suggests the latter is applicable (Zhu et al., 2006). The exception might be imprinting disorders like Beckwith–Wiedemann syndrome (Lim et al., 2009); however, the absolute frequency of imprinting defects remains low even if relative risk is increased.

No differences were found by Liebaers et al. (2009) in structural malformations between PGD offspring and ICSI offspring—2.13 versus 3.38%, respectively. Further, there were no differences between offspring resulting from single-gene PGD and PGD aneuploidy testing, for which reason data were merged. There proved to be no differences in singletons with respect to stillborns, live births, or neonatal deaths. Multiple gestations PGD offspring showed increased perinatal deaths, for reasons that are unclear. Updated at the 2009 Preimplantation Genetic Diagnosis International Society (PGDIS) meeting, the major congenital anomaly rate in the Reproductive Genetics Institute (Chicago) was similar—1.9% of 1230 babies (Ginsberg et al., 2009). In no study have anomalies been disproportionately clustered in any given organ system in either cohort, further offering assurance.

Diagnostic accuracy is high, the error rate of Liebaers et al. (2009) being 0.6% after excluding a well-described case in which linkage analysis was incorrectly deduced (Sermon et al., 1998). Rechitsky et al. (2009) reported the Reproductive Genetics Institute error rate for
single-gene disorders to be 0.3% per transfer cycle among 1666 cycles involving 202 different genetic conditions.

Actually, safety is to be expected. The corollary of the toti-potential nature of the early embryo dictates that removal of a single cell (or two) should cause no irreparable damage because no single cell is committed along a given developmental pathway. Loss of one or more blastomeres should not lead to an increase in anomalies in surviving offspring, even if it might lead to lower implantation rates.

Of note is that embryo biopsy practiced by the Brussels center is not necessarily that employed elsewhere. That two rather than one blastomere was often removed (Staessen et al., 2004) has previously received comment (Cohen and Grifo, 2007; Simpson, 2008). Implantation rates appear to be lowered by removal of two blastomeres based on data from cryopreserved embryos that are thawed (Cohen et al., 2007); however, this does not necessarily translate to an increased frequency of anomalous live births. Similarly, polar body biopsy followed by blastomere biopsy seemingly does not appear to decrease pregnancy rate, nor should it result in increased structural anomalies. Selection against any damaged embryo, biopsied or not, is strong.

Is this study ideal? Will the ‘evidence-based’ aficionados be satisfied? Of course not. A much larger sample size, namely thousands if not tens of thousands, is necessary to exclude categorically an increase of anomalous live borns. Similarly, polar body biopsy followed by blastocyst biopsy does not result in increased birth defects. By extrapolation and analogous data, the same should apply to polar body or blastocyst biopsy. PGD is highly accurate (>99%). Whatever the controversy concerning efficacy of PGD in increasing pregnancy rates, patients may be informed that PGD is safe.

References


Cohen J, Well D, Munné S. Removal of 2 cells from cleavage stage embryos is likely to reduce the efficacy of chromosomal tests that are used to enhance implantation rates. Fertil Steril 2007;87:496–503.


