Preimplantation genetic diagnosis for an insertional translocation

Sir,

Melotte et al. (2004) present two unsuccessful cycles of preimplantation genetic diagnosis (PGD) for a couple where the female partner carries an interchromosomal insertional translocation of part of the long arm of chromosome 2 into the long arm of chromosome 14. The authors present an elegant proof showing that it may be necessary to incorporate up to four probes into a PGD test for insertional translocations; this can be challenging because of the limited number of fluorochromes and haptnets, and suitable ready-to-use commercial FISH probes are generally not available for the interstitial inserted segment of this type of rearrangement. The approach presented by the authors is comprehensive and is an important reference paper for practitioners interested in PGD for insertional translocations.

However, accurate interpretation of the results is significantly impaired by the lack of confirmation of diagnosis studies using the remaining cells from the embryos that were not transferred. The interpretation of the insertional translocation status of the embryos is based only on one or two nuclei, and must be expected to be subject to error associated with the mosaic nature of cleavage stage embryos and the FISH assay (the authors quote 91% specificity in lymphocytes). The diagnosis of two embryos being consistent with 3:1 segregation on the basis of a single deviant FISH signal may therefore represent simple error associated with the FISH assay (the diagnosis is stronger for the embryo where there were two informative signals). The authors assert that one embryo remained without a diagnosis, despite having a consistent signal pattern in two nuclei, because the pattern did not conform to any of the permutations in their model; the authors acknowledge that this result could be interpreted as a suggest that this insertional translocation is segregating in any way other than normal independent segregation of the two bivalents resulting in a 1:1:1:1 gamete ratio (normal : balanced : duplication : deletion) (Gardner and Sutherland, 2004). The chromosome imbalance associated with the two live born children and the aborted fetus (trisomy for the inserted segment 2q31→2q35; monosomy would be expected to be less viable) is consistent with normal segregation, or 2:2 segregation following zero or an even number of crossovers if a quadrivalent is formed. It is therefore also intriguing that none of the ten embryos tested appear to be consistent with the duplication/deletion forms of the insertion. There is of course the possibility that some of the embryos diagnosed as normal or balanced in the absence of confirmation of diagnosis studies may have been misdiagnosed due to the limitation of the FISH test that would require only a single signal scoring error.

The inserted segment may be large enough to allow the formation of a quadrivalent, and therefore 3:1 segregation must be considered to be a possibility. However, in the absence of confirmation of diagnosis studies, the data presented are probably not convincing given the limitations of FISH applied to only one or two nuclei. Confirmation of diagnosis studies is essential for accurate cytogenetic interpretation of the chromosome complement of an embryo and is recommended for all embryos not transferred or cryopreserved following diagnosis, to provide quality assurance and misdiagnosis rates to PGD patients (Thornhill et al., 2004).

References


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doi:10.1093/humrep/deh693

Pregnancy outcome after blastocyst transfer as compared to early cleavage stage embryo transfer

Sir,

We have read with great interest the retrospective cohort study on the possible benefit of blastocyst transfer (BS group) compared to cleavage stage transfer (CS group) on day 2–3 by Schwärzler et al. (2004).