The use of ICSI provides an effective treatment for severe male factor infertility (1). The negative effects of abnormal semen characteristics and sperm quality on fertility can be overcome with ICSI if viable sperm are available because the technique bypasses the zona pellucida and oolemma to deliver the male chromosomes directly into the ooplasm. ICSI allows couples with male factor infertility to achieve live birth rates comparable to those achieved with in vitro fertilization (IVF) using conventional methods of fertilization. ICSI can be performed even in men with azoospermia if spermatozoa can be successfully collected from the epididymis or the testis (2–4). ICSI is compatible with normal embryonic development (5, 6), and is no longer regarded as an experimental procedure (7).

Reports on the risk of congenital malformations associated with ICSI, compared to those associated with conventional fertilization in IVF cycles, have yielded conflicting results. (8–13). At least in part, differences in sample size and patient demographics might help to explain the differing conclusions. The most comprehensive multicenter study conducted thus far, based on data from five-year-old children, has suggested that ICSI is associated with an increased risk of certain major congenital anomalies (14). However, whether the association relates to the ICSI procedure itself, or to inherent sperm (or even possibly egg) defects, could not be determined because the study did not distinguish between male factor conditions and other causes of infertility. Although the possibly increased risk of congenital malformations in children conceived with ICSI is relatively low (4.2%), the information is nonetheless important and should be shared with patients considering such treatment. The intellectual and motor development of children conceived via ICSI also has been controversial. An early report suggested that development in such children lagged significantly behind that of children resulting from conventional IVF or those conceived naturally (15). However, more recent studies from larger groups, using standardized criteria for evaluation, have not detected any differences in the development or the abilities of children born after ICSI, conventional IVF, or natural conception (16–18).

The prevalence of sex chromosome abnormalities in children conceived via ICSI is higher than observed in the general IVF population (19–26), but the absolute difference in prevalence between the two groups is relatively small (0.8% to 1.0% in ICSI offspring vs. 0.2% in the general IVF population). The explanation for the increased prevalence of chromosomal anomalies observed in ICSI offspring is not clear. Whereas it may result from the ICSI procedure itself, it might also reflect a direct paternal effect. Men with oligozoospermia, asthenozoospermia, or teratozoospermia often exhibit an increased level of sperm aneuploidy; the sex chromosomes (X and Y) in the sperm of men with abnormal semen parameters appear especially prone to aneuploidy (27–32). These observations offer a possible explanation for the increased risk of sex chromosome abnormalities observed in conceptions resulting from ICSI. The prevalence of translocations of paternal origin and of de novo balanced translocations in ICSI offspring (0.36%) also appears higher than in the general population (0.07%) (33).

Congenital bilateral absence of the vas deferens (CBAVD) is highly associated with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. (34, 35). In addition, Y chromosome microdeletions, in the azoospermia factors (AZF) region, have been observed in between 3% and 15% of men with severe oligozoospermia and non-obstructive azoospermia (36). Since pregnancy can be achieved in couples wherein the male partner harbors such abnormalities, the risk that male offspring might later manifest disorders including infertility is very real. The extent to which abnormal paternal genotypes such as CF mutations, Y chromosomal microdeletions, or Klinefelter syndrome (37) might be transmitted to offspring conceived with ICSI, and the ultimate impact they may have on their phenotype is not yet clear. Y chromosomal microdeletions will be transmitted to male offspring if a Y-bearing sperm is used for ICSI (38, 39). However, men without a detectable deletion also can generate offspring having a Y chromosome microdeletion (38), due to a genomic discrepancy between somatic cells and germ cells (40) in which a mosaic genome or a deletion arises de novo, most likely at the post-zygotic stage (38). Although the outcome remains uncertain, it is assumed that an infant inheriting such a microdeletion might be azoospermic,
and the possibility of a more severe expression of the gene mutation cannot be excluded.

The specific location of an AZF microdeletion has prognostic value regarding the likelihood of obtaining spermatozoa from an affected man. Most men with microdeletions in the AZFc region of the Y chromosome exhibit either severe oligospermia or azoospermia, but 70% are nonetheless likely to have sufficient sperm production to allow sperm extraction via testis biopsy (41). If spermatozoa can be obtained from such patients, they are functionally competent to achieve fertilization and normal pregnancies, but will also transmit the deletion and its associated infertility to any male offspring (41, 42). In contrast, microdeletions involving the AZFb or AZFa regions of the Y chromosome predict a very low probability for successful sperm extraction even with extensive testicular biopsies (43), and patients having such abnormalities must be counseled accordingly.

SUMMARY AND RECOMMENDATIONS

- ICSI appears to be a safe and effective therapy for the treatment of male factor infertility.
- Certain conditions may carry an increased risk for transmission of genetic abnormalities to offspring via ICSI.
- Whether the increased prevalence of genetic abnormalities observed in ICSI offspring relates to the procedure itself, or to the characteristics of couples who require ICSI to conceive, is unclear.
- Couples with male factor infertility considering ICSI should be counseled about the associated potential risks.
- When specific genetic abnormalities (e.g., abnormal karyotypes, Y chromosome microdeletions, CF mutations) are identified, affected couples should receive appropriate genetic counseling before proceeding with treatment. Only those fully apprised of risk for transmitting a genetic defect and its potential effect on their offspring should be offered ICSI.
- Other genetic testing before embryo transfer (preimplantation genetic diagnosis) or during early pregnancy (amniocentesis or chorionic villus sampling) may be appropriate in selected cases.

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