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Risk of transmission of genetic diseases by assisted reproduction

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Infertility devastates the life plans of 8%–12% of couples attempting to conceive for the first time. In about half of these cases a male factor is causative. Interestingly, research in male reproduction over the past 30 years has focused largely on the endocrine control of spermatogenesis and genital tract function, yet only about 1% of male infertility has an endocrine cause; thus, this research has had little effect on the treatment of the infertile male. With advancements in molecular medicine, researchers are now beginning to dissect the genes required for male fertility, although their approaches predominantly take advantage of ever-expanding collections of mouse models.[1] The advent of surgical sperm collection from the epididymis or testis and the development of intracytoplasmic sperm injection (ICSI) have provided the only major technological advances in recent years.

While most textbooks state that approximately 30% of male infertility is idiopathic, some experts speculate that perhaps 50% of all male infertility is idiopathic. In part, this speculation reflects our poor understanding of the basic mechanisms that regulate genital tract differentiation and development, spermatogenesis, sperm maturation in the genital tract, and the molecular events required for fertilization and early embryonic development; and, hence, our inability to properly diagnose the cause of the infertility. Indeed, commonly used diagnostic categories for male infertility are descriptive and not usually mechanistically based. Accordingly, our ability to properly diagnose and counsel male factor infertile couples is limited. Nevertheless, research shows that genetic defects in male factor infertility are more common than originally believed. These findings have raised concerns that since the assisted reproductive technologies essentially overcome the natural barriers to defective sperm fertilization, mechanisms may now be bypassed that prevent the transmission of genetic defects to offspring of these genetically infertile men.

Recognizing this diagnostic limitation, there are nevertheless important clinical genetic tests that should be used today in the diagnosis of the infertile male. The karyotype remains the gold standard of chromosomal analysis and provides important insights regarding the presence of both numerical and structural chromosome abnormalities. Although chromosomal abnormalities are uncommon in fertile men, routine karyotyping suggests that these abnormalities are present in about 6% of infertile men.[2] Defects include human trisomies that result from aberrant recombination during gametogenesis such as sex chromosome abnormalities, which are among the most common human trisomies.[3] For

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example, Klinefelter syndrome occurs in 1 per 500 live male births[4] and affects approximately 14% of men with nonobstructive azoospermia, making this trisomy one of its most common causes.

The recent molecular revolution in genetics provides the cytogeneticist with an array of methods to diagnose structural chromosomal defects using such technologies as fluorescent *in situ* hybridization (FISH), chromosome painting, and comparative genomic hybridization, as well as polymerase chain reaction (PCR) and direct DNA sequencing. Structural defects include balanced and unbalanced translocations as well as inversions and deletions. Using karyotype analysis, Gekkas *et al.*[5] reported that 6.1% of unselected men (134 of 2,190) who needed ICSI had a somatic chromosomal rearrangement. The frequency of somatic (blood) chromosome abnormalities was higher in men with azoospermia (18.71%) than in men with severe (14.55%) or moderate (2.37%) oligozoospermia. Accordingly, men with azoospermia and oligospermia ($<5 \times 10^6$ sperm/ml) and men seeking to achieve a pregnancy with ICSI should be tested for chromosome defects, at the very least with a karyotype analysis.

Another common structural defect in men with nonobstructive azoospermia or severe oligospermia is a deletion within the Y chromosome. A region at Yq11, deleted in several infertile men, was identified by cytogenetics over 25 years ago and termed the Azoospermia Factor Region (AZF).[6] This region (now further subdivided into AZFa, b, and c), includes several genes involved in spermatogenesis, such as the gene termed “deleted in azoospermia” (DAZ).[7] The deletion frequency of this region in azoospermia and severe oligospermia varies, but it is generally accepted that the incidence of deletions in azoospermic men is approximately 8%–11%, and lower in severely oligospermic men.[8] Most state-of-the-art andrology laboratories employ a multiplex-PCR-based assay to diagnose men with nonobstructive azoospermia and men with severe oligospermia for Y chromosome micro-deletions. Y-deletion analysis, therefore, should be offered to all azoospermic men and those with sperm densities $<5 \times 10^6$ sperm/ml.

Although most genetic testing available in the US for infertile men analyzes somatic cells to define chromosomal or structural abnormalities or specific genetic syndromes, such as congenital bilateral absence of the vas deferens (CBAVD), gonosome aneuploidy represents a major cause of male infertility as well. FISH provides insight into the aneuploidy present in sperm from infertile men who have a normal somatic karyotype.[9,10] The incidence of aneuploidy increases as semen quality decreases,[11] and even men with nonobstructive azoospermia have an increased incidence of germ cell nondysjunction.[12] Accordingly, those men with severe oligospermia ($<5 \times 10^6$ sperm/ml) and nonobstructive azoospermia should be screened for gonosome aneuploidy. In addition, men who are partners of couples with recurrent pregnancy loss are thought to be at increased risk for gonosome aneuploidy. Preimplantation Genetic Diagnosis (PGD) used in combination with ICSI might help these genetically abnormal couples achieve a normal pregnancy.

CBAVD, observed in 1%–2% of infertile males and men with cystic fibrosis, is a genital form of cystic fibrosis that occurs because of a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[13] Diagnosis of these patients is challenging for the urologist, because the majority of clinical genetics laboratories offer testing for the most common mutations in the CFTR gene associated with cystic fibrosis development, but not for CBAVD. Complete mutation analysis of the very large CFTR gene is available in only a few clinical laboratories in the US. In addition, a polymorphism of the CFTR gene (the 5T allele) that modulates disease severity is frequently associated with CBAVD. For these affected couples, it is critical that the female partner be assessed for common cystic fibrosis mutations; even with a normal result, the couple is at increased risk of conceiving a child with cystic fibrosis. Men with unexplained epididymal obstruction and

ejaculatory duct obstruction also have an increased risk for CFTR mutation and should be tested.

Finally, there are genetic syndromes that are characterized by infertility or diminished reproductive fitness. These syndromes include several of the triplet repeat diseases (e.g. Kennedy syndrome), reproductive endocrinopathies, sperm-function anomalies, and genitourinary developmental defects.[1] While many of these syndromes are well recognized and the genetic basis is clearly understood, they are not always considered as a possible etiology in the evaluation of infertile men.

When found, genetic counseling has now become an important part of interpreting the significance of these genetic abnormalities associated with male infertility. Despite major advances in our ability to diagnose genetic defects, couples need to understand that of the 1,005 genetic diseases for which clinical laboratory testing is available, it is impossible to screen an embryo for each known defect. For both fertile and infertile couples, current technologies can still not ensure the birth of a “perfect” baby.

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