Genetic counseling to infertile patients

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Assisted reproductive technologies (ART) have improved during the last 20 years to the point of allowing an increasing number of previously non-fertile couples to reproduce successfully. Baby Louise Brown (the first test tube baby) is now a healthy 25 years old lady. In 1978 her birth, after a successful in vitro fertilization (IVF) procedure in a case of fallopian tubal blockage, was saluted as a major achievement in the treatment of human infertility. Since then IVF has moved from a technology capable of bypassing mechanical obstacles by permitting the encounter of gametes in cases of tube obstruction to a much more sophisticated group of technologies that allows treatment of more severe forms of infertility. Intracytoplasmatic sperm injection (ICSI) was introduced clinically in 1991 and was coupled to even more daring techniques such as MESA (Microsurgical Epididymal Sperm Aspiration) or TESE (Testicular Sperm Extraction). These techniques revolutionized the treatment of male infertility for which up to then very little could be done. By 1995, over 20 000 children had been born worldwide by means of the ICSI technique (de Mouzon 1997). Very little formal evaluation of its possible effects on the health of the children conceived by these means was performed before its clinical introduction.

Research work on human infertility, generally dedicated to the study of female gametes, has become since then more focused on the study of human spermatozoa but this happened well after the wide application of the ICSI technology. Human male gametes were and still are classically studied by utilizing parameters such as sperm

concentration, motility and morphology, which today are known to define only partially sperm quality.

Spermatozoa utilized for the ICSI procedure are at best subjectively judged of good quality according to these parameters and in extreme cases even immature or below standard sperm is used if the only available, (i.e. in MESA or TESE cases).

This attitude is in fact based on the dogma that an all or no effect phenomenon exists at fertilization capable of eliminating “bad sperm”. As we will see this is far from having been demonstrated and rather opposite data are appearing in the literature. Quite a lot of research has since been performed on the subject with a variety of experimental approaches.

RISK OF MAJOR AND MINOR BIRTH DEFECTS IN THE BABIES BORN AFTER ICSI AND IVF

In general early studies had not shown an increased risk of major birth defects for either techniques (Bonduelle 1998). The incidence of major malformations detected at birth or during the perinatal period in these early studies was reported to range between 0.95% and 3.6%, not significantly different from that observed in the general population. These early surveys, though, suffered of methodological biases such as small sample sizes, inadequate control groups or ambiguous or different definitions of major and minor birth defects. Indeed some data could well show a slight increase in anomalies of the offspring (Kurinczuk 1997). Since 1995 a possible increase in sex chromosome anomalies (SCA) (1% in ICSI babies compared to 0.25 to 0.5 % in the general population) had already been reported (In’t Veld 1995). Moreover recent data seem to confirm an excess risk of major birth defects. Hansen *et al.* (2002) have reported an increase of major birth defects particularly for cardiovascular, urogenital, musculoskeletal and chromosomal defects for both procedures with a risk evaluated as twice that of normal conception. Urogenital

defects and in particular hypospadias have also been reported to be in excess in ICSI babies with a relative risk of 3.0 (Wennerholm 2000). This increase in abnormalities could be due to many different reasons such as the relatively advanced age of infertile couples, the medications used to induce ovulation or sustain the early stages of the pregnancy, to the in vitro procedure, at all stages and particularly at the time of the microinjection of the spermatozoon in the ooplasm, and last but not least the underlying causes of infertility.

Follow up of the offspring is now being routinely performed by many of the larger infertility centers (Bonduelle1998; Bowen 1998; Palermo 1996).

Genetic and epigenetic origin of infertility

Many current indications for ICSI are indeed associated with hereditary disorders which might not be perpetuated otherwise. Klinefelter syndrome and its mosaicisms, structural chromosomal aberrations (such as translocations), Y-chromosome microdeletions, mutations of the cystic fibrosis transmembrane conductance regulator gene, androgen receptor gene mutations, globozoospermia (round headed sperm), immotile cilia syndrome, Kallmann syndrome.

As research continues more knowledge is accumulating such as the implication of Dna mismatch repair gene PMS2 in azoospermia in mice or of incomplete genomic imprinting in spermatids. Human homologous genes might exist.

For all of these reasons ART patients must be informed and must undergo in my and many other’s specialists opinion a complete genetic screening (couple’s karyotyping, search for Y microdeletions and mutations for CRTL genes) and extensive genetic counseling.

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