Intracytoplasmic sperm injection pregnancy with fetal trisomy 9p resulting from a balanced paternal translocation

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Case report

The couple was referred for prenatal diagnosis after an ICSI procedure had been performed in an outward institution. The reason for ICSI was male factor infertility. Both partners had been karyotyped before treatment was begun. Chromosome analysis had shown a normal karyotype in the female and a balanced reciprocal translocation, 46,XY,t(1;9)(q44;p11.2) in the male partner. The couple was advised about a possible risk for a chromosomally unbalanced pregnancy, and a risk estimate of 5–10% for such an unfavourable outcome was given. In the first ICSI attempt two embryos were transferred and an diamniotic twin pregnancy developed.

Amniocentesis was carried out in the 15th week of pregnancy. The female twin A was found to have normal chromosomes, 46,XX while the male twin B had an unbalanced karyotype, 46,XY,der(1),t(1;9)(q44;p11.2),pat resulting in trisomy for almost the complete short arm of chromosome 9 (Figure 1). A detailed ultrasound study did not reveal any abnormalities in either of the twins. The parents wished confirmation of the cytogenetic diagnosis by cord blood analysis. Cordocentesis of both twins was carried out, and karyotyping of lymphocytes confirmed the amniocentesis results. After extensive genetic counselling the couple opted for selective termination of the twin B pregnancy. The twin A pregnancy has taken an uneventful course since.

Introduction

The genetic safety of intracytoplasmic sperm injection (ICSI) and related techniques is a central issue in the debate about risks of micro-assisted human reproduction (Meschede et al., 1995; Baschat et al., 1996a; Chandley and Hargreave, 1996; Martin, 1996; Persson et al., 1996). One reason for concern is that constitutional chromosomal abnormalities have a significantly higher prevalence among infertile men than in unselected male newborns (Bourrouillou et al., 1985; De Braekeleer and Dao, 1991). While in azoospermic patients numerical anomalies of the sex chromosomes predominate, structural rearrangements such as translocations or inversions are the most common chromosomal aberrations in oligozoospermic men. Not only do such structural abnormalities interfere with male gametogenesis and cause subfertility (Chandley et al., 1986), they also carry a risk for chromosomal malsegregation during meiosis. A variable proportion of sperm of translocation or inversion carriers are endowed with an abnormal set of chromosomes (Martin, 1995), and this may ultimately result in chromosomally unbalanced pregnancies. As male factor subfertility represents the most important indication for ICSI, structural chromosome anomalies are not an uncommon finding among patients treated with this modality. We report the first case of a pregnancy conceived through ICSI where a paternal translocation resulted in an unbalanced fetal karyotype.

Discussion

The rate of chromosomal anomalies among patients enrolled in ICSI programmes is clearly higher than in the general population (Baschat et al., 1996b; Bonduelle et al., 1996; Testart et al., 1996). Many centres routinely karyotype both or at least the male partner before ICSI treatment is initiated. Patients with an abnormal karyotype should undergo thorough genetic counselling as certain chromosomal aberrations such as reciprocal translocations carry a substantial risk for meiotic malsegregation and the production of chromosomally abnormal gametes.

In pregnancies of reciprocal translocation carriers three possible outcomes may occur: (i) only the two normal homologues of the involved chromosome pairs are passed on – in this case, the embryo will have a normal karyotype; (ii) only the translocation chromosomes are passed on – the embryo will carry the same translocation as one parent, but no adverse effects (apart from possible later subfertility) are to be expected. There is a structurally abnormal, but balanced karyotype; (iii) one of the normal homologues and one of the translocation chromosomes is passed on – here, a structurally abnormal and unbalanced set of chromosomes will result. This can either
lead to a spontaneous abortion due to gross imbalance in the karyotype or to a viable fetus with trisomy and/or monosomy for certain parts of its genome. To the best of our knowledge this is the first reported instance where the latter outcome has been observed in a pregnancy conceived through ICSI.

Trisomy for the short arm of chromosome 9 as diagnosed in twin B is compatible with survival to term. The literature contains more than 100 postnatally recorded cases (Schinzel, 1994). In fact, trisomy 9p is one of the clinically well characterized types of aneuploidy in the human (Jones, 1988). Mental retardation, often to a severe degree, is a virtually universal finding, and 40% of individuals with trisomy 9p are microcephalic. In contrast, major structural malformations are the exception rather than the rule. Congenital heart disease or cleft lip and palate are observed in 10% or less of affected individuals. Mild orthopaedic problems appear to be fairly common, and some minor physical dysmorphisms are present in most patients. In our prenatally ascertained case, no physical anomalies of the fetus could be detected by meticulous ultrasound scanning. This is not an unexpected finding considering the absence of major structural anomalies in most of the postnatally examined cases. As a selective termination in an ongoing pregnancy was carried out no autopsy of the aneuploid fetus could be performed.

A question frequently asked by translocation carriers is exactly how large the risk is of a chromosomally abnormal pregnancy or child. Empiric data for a few common translocations are available, but more often than not one is left without such ready-made figures. A crude risk estimate may be arrived at by applying some general rules of thumb about the meiotic behaviour of structurally abnormal chromosomes (Gardner and Sutherland, 1996). However, whether these or the empiric risk figures are used, they are all based on experience of naturally conceived pregnancies. This makes their application to the ICSI setting problematic, as under the conditions of micro-manipulation another population of gametes may be selected for fertilization than under natural circumstances. We therefore suggest that infertile translocation carriers in ICSI programmes should be advised that the risk figures currently available for an aneuploid pregnancy may not apply to their situation, and that at least theoretically a higher risk cannot be excluded until more data from ICSI pregnancies become available.

References

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