Sex chromosomal anomalies in pregnancies conceived through intracytoplasmic sperm injection: a case for genetic counselling

D. Meschede and J. Horst

Institute of Human Genetics, Vesaliusweg 12–14, D-48149 Münster, Germany

To whom correspondence should be addressed

Introduction

Intracytoplasmic sperm injection (ICSI) has markedly improved the chances for successful treatment of male factor infertility by assisted reproductive technology (Van Steirteghem et al., 1996). The issue of possible genetic risks of this new and powerful procedure has attracted considerable attention (Meschede et al., 1995). One important aspect in the debate about genetic implications is the presumably increased rate of sex chromosomal anomalies (SCA) in ICSI pregnancies. Recently In’t Veld et al. (1995) reported that among 15 fetuses that were conceived through ICSI they detected five SCA: 45,X and 47,XXY twice each, and one complex mosaic 45,X/46,X,dic(Y)/46,X,del(Yq). Due to the small number of cases these results cannot be directly extrapolated to larger patient populations. Data from the Free University of Brussels’ ICSI programme suggest that the rate of sex chromosomal anomalies in ICSI fetuses may actually be at around 1% (Liebaers et al., 1995; Van Steirteghem et al., 1996). These investigators found five cases in a total of 585 prenatal diagnoses – 47,XXY twice, 47,XXX, 47,XYY, and one instance of 46,XX/47,XXX mosaicism. Compared with unselected and naturally conceived liveborn babies this is a frequency of SCA increased by a factor of four (Hsu, 1992). It is also higher than the SCA rate among the fetuses of women undergoing amniocentesis for indications other than ICSI. If only women 35 years and older who carried a naturally conceived pregnancy and underwent amniocentesis are considered for comparison, the SCA rate in this cohort is 0.43%, clearly lower than among ICSI pregnancies (Ferguson-Smith and Yates, 1984).

Dealing with SCA is a regular task for the clinical geneticist. In our institution we have accumulated extensive experience in counselling patients affected with SCA themselves, as well as prospective parents expecting a child with such an anomaly.

Key words: intracytoplasmic sperm injection/sex chromosomal anomalies/developmental prognosis/genetic counselling

Discussion

What can such prospective parents be told about the developmental perspectives of their child? For such counselling it is pivotal that only data from studies with an unbiased and prospective mode of proband ascertainment are used. By now, a solid database exists on individuals with an SCA diagnosed through cytogenetic mass screening of newborns or incidentally on occasion of an amniocentesis. Follow-up of such cohorts into young adulthood has been achieved in long-term developmental studies conducted in the USA, Canada, Scotland and Denmark (Evans et al., 1990). While the results differ somewhat in detail, the general picture is quite uniform.

If very rare variants such as gonosomal structural aberrations and mosaics are disregarded, SCA can be conveniently grouped on one hand and Turner syndrome (also Ullrich-Turner syndrome) on the other. Turner syndrome (45,X) is the only
numerical SCA associated with some structural malformations. The following figures apply to liveborn girls with a 45,X karyotype, who constitute 53% of patients with Turner syndrome (Hook and Warburton, 1983). They have short stature (98%), mostly benign urological anomalies (45–60%) and heart or aortic anomalies (20–30%), some requiring surgical correction (Hall and Gilchrist, 1990). Infertility and lack of pubertal development is the rule, although a few patients have achieved and carried to term a pregnancy (Kaneko et al., 1990). There is no increased rate of mental retardation, but motor and language development may be delayed, and 50% or more of these individuals need special academic support (Robinson et al., 1992). It is important to counsel the prospective parents about the high rate of spontaneous pregnancy loss in Turner syndrome. Whereas 1% of all human concepti may have the karyotype 45,X, this anomaly is found in only one of 5000 liveborn girls (Hall and Gilchrist, 1990). If Turner syndrome is diagnosed in the first trimester through chorionic villus sampling there is a very high likelihood that the pregnancy will not be carried to term, especially if sonographic abnormalities are already apparent. If the diagnosis is made in the second trimester by amniocentesis, the rate of spontaneous abortions or stillbirths is still 82% (Hook, 1983).

The spontaneous loss rate is also increased in XXY fetuses, but not so in concepti with an XYY or XXX chromosomal complement. Postnatal somatic development is largely normal with the notable exception of infertility and testosterone deficiency in men with Klinefelter syndrome. XXX and XYY individuals often remain undiagnosed for their lifetime, and it is rare for patients with Klinefelter syndrome to be ascertained before the expected time of puberty. XXY, XYY and XXX individuals have an average intelligence quotient (IQ) about 10–15 points lower than controls with a normal karyotype. (Nippert, 1990). SCA in most cases are not associated with learning that an unborn child carries an SCA is a distressing experience for expectant parents. As in all other prenatally diagnosed disorders, full and detailed information about the condition under discussion is the primary need of such couples (Nippert, 1990). There is no increased rate of mental retardation, but most of these individuals need special academic support. The prognostic significance of a prenatally diagnosed SCA should neither be downplayed nor overstated. It is our experience that with careful genetic counselling parents often adapt rapidly to the information that their child carries an SCA, they appreciate these children, and most are highly motivated to take an active role in managing academic or physical problems should they occur. Terminating an ICSI pregnancy for which an infertile couple may have struggled through many years is always a medical and human catastrophe. This is even more true if the reason is an SCA. While the final choice about continuation or termination of a pregnancy should always remain with the parents, it is the obligation of the counsellor to provide a realistic – and this for most SCA parents often adapt rapidly to the information that their child carries an SCA, they appreciate these children, and most are highly motivated to take an active role in managing academic or physical problems should they occur. Terminating an ICSI pregnancy for which an infertile couple may have struggled through many years is always a medical and human catastrophe. This is even more true if the reason is an SCA. While the final choice about continuation or termination of a pregnancy should always remain with the parents, it is the obligation of the counsellor to provide a realistic – and this for most SCA is a mostly optimistic – picture of the condition to be expected in the offspring.

**References**


Bender et al. (1993) give full-scale IQ of 96.3 and 84.4 for XXY and XXX individuals and 106.4 for their controls. It is important to remember that the normal range for the IQ spans from approximately 70–130, i.e. 2 SD from the population mean of 100. Whereas academic problems are clearly more prevalent among XXY, XYY and XXX individuals, the rate of mental retardation is not increased above the population baseline. Diminished full-scale IQ and poorer academic achievements are mainly the result of deficits in verbal ability (Rovet et al., 1995).

Much attention has been given to the reportedly increased rate of criminal behaviour among XYY individuals. While the 47,XYY karyotype may actually be somewhat more prevalent among prison inmates and petty criminals than in the general population (Witkin et al., 1976), it needs to be emphasized that the majority of XYY men lead normal lives and are socially well adapted. Boys with a 47,XYY chromosomal complement may show more temper tantrums and a lower frustration tolerance than other children (Robinson et al., 1991). Two recent studies show that a significant proportion of pregnancies with SCA are terminated. Robinson et al. (1989) report induced abortion rates of 45, 32 and 35% for XXY, XYY and XXX pregnancies respectively. Their study cohort comprised 252 cases, and counselling was carried out by telephone contact with either the pregnant woman herself or her medical caretaker. In a smaller series including 26 prenatally diagnosed SCA cases, Holmes-Siedle et al. (1987) give termination rates of 66, 33 and 37% for the XXY, XYY, and XXX karyotypes. Here, patients were directly counselled by either an obstetrician or a geneticist.


Received on January 10, 1997; accepted on April 10, 1997