CASE REPORT

Paternal origin of trisomy 21 following intracytoplasmic sperm injection (ICSI)

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One important aspect in the debate on the genetic risks associated with intracytoplasmic sperm injection (ICSI) is the possible increased rate of chromosomal abnormalities in resulting pregnancies. ICSI was performed in a 27 year old man with asthenoteratozoospermia and his 25 year old wife. There was a spontaneous miscarriage at 9 weeks of gestation. Cytogenetic investigation revealed trisomy 21. Analysis of two polymorphic microsatellite markers showed that the additional chromosome was paternal. This is in contrast to the fact that the vast majority of trisomic concepti are maternal in origin. Identifying the parent of origin in trisomic conceptions achieved by ICSI may reveal whether ICSI is associated with an increased risk of paternally derived aneuploidy.

Key words: genetic risk/intracytoplasmic sperm injection/male infertility/pregnancy loss/trisomy

Introduction

Since the introduction of intracytoplasmic sperm injection (ICSI) as an effective procedure to overcome male factor infertility, caution about genetic risks has been advised. It has been argued that bypassing natural sperm selection which occurs when spermatozoa penetrate into the oocyte may promote fertilization by genetically abnormal spermatozoa. One of the genetic risks possibly associated with ICSI is an increase of aneuploid concepti.

Literature data on chromosomal anomalies after ICSI are ambiguous (I’nt Veld et al., 1995; Bonduelle et al., 1996; Palermo et al., 1996; Van Opstal et al., 1997). The incidence of gonosomal aberrations in second trimester fetuses might be slightly increased (Liebaers et al., 1995; Bonduelle et al., 1996). However, the available cytogenetic data of prenatal diagnoses and clinical pregnancy losses occurring after ICSI are limited.

One possible explanation for the proposed higher incidence of chromosomal aberrations could be due to a higher number of sperm cells with chromosomal abnormalities in infertile men. In spermatozoa of infertile men with normal somatic karyotype studied by fluorescence in-situ hybridization (FISH) a slightly higher rate of numerical sex chromosome abnormalit-ies was observed (Martin, 1996; Lähdetie et al., 1997). More recently, Colombo et al. (1997) reported an increased rate of disomy for chromosomes 18 and 21 in spermatozoa from infertile men. They concluded that paternal disomy may be responsible for some cases of trisomy 21 in the offspring of subfertile men.

We report, to our knowledge, the first case of a paternally-derived trisomy 21 in a conceptus conceived by ICSI.

Case report

A 27 year-old man with asthenoteratozoospermia and his 25 year old wife with a 3 year history of primary sterility and one unsuccessful attempt of in-vitro fertilization (IVF) were referred to our ICSI programme. Prior to ICSI, chromosome analyses were performed on G-banded lymphocyte chromosomes from both patients (approximately 500 band stage). The karyotypes were normal. A pregnancy was achieved after ICSI. However, at 9 weeks of gestation the patient suffered a spontaneous miscarriage. Chromosomes of the conceptus were analysed after semidirect preparation and long-term culture of chorionic villi. The G-banded karyotype was found to be 47,XY, +21 in three and seven mitoses respectively, without any hint of mosaicism.

The parental origin of the additional chromosome 21 was assessed using two polymorphic microsatellite markers, a tetranucleotide repeat (D21S11) and a dinucleotide CA-repeat (D21S269) from 21q21 and 21q22 respectively. The allele size was determined using polymerase chain reaction (PCR) amplification of the microsatellite repeats and subsequent electrophoresis on an ABI 373 DNA sequencer. The observed alleles are shown in Table I. Two different paternal alleles and one maternal allele were found in the conceptus for both markers. This pattern is consistent with non-disjunction during the paternal first meiotic division.

Discussion

The genetic safety of ICSI as a novel procedure of assisted fertilization may be assessed by the rate of children born with chromosomal abnormalities. In naturally conceived pregnancies, only 5–9% of trisomy 21 were found to be paternally transmitted, and the vast majority of trisomies are of maternal origin (Antonarakis, 1991; Yoon et al., 1996). This relationship was found in both newborns and aborti. This observation and the frequency of trisomy 21 (approximately 1 in 700 live births; Cuckle et al., 1987) impedes the epidemiological
analysis of a potential increase of aneuploidy induced by microinjection. To detect the effect of, e.g. a two-fold increase of paternally-derived trisomy 21 to a newborn population, more than 450,000 pregnancies would have to be studied after ICSI.

Another approach is to determine the parent of origin in cases of aneuploidy. If trisomy in an ICSI-derived pregnancy is due to disomy in the spermatozoa, the supernumerary chromosome should be of paternal origin. In the present case the trisomy was indeed paternally derived. To our knowledge there is only one study dealing with the parental origin of aneuploidies in ICSI pregnancies of infertile men with normal karyotype; nine abnormal karyotypes were found after prenatal diagnosis of 71 fetuses conceived by ICSI. Each of the six autosomal anomalies was of paternal origin and the two gonosomal anomalies was of paternal origin and the two autosomal trisomies were of maternal origin. No fetal DNA was available in one case (Van Opstal et al., 1997).

However, considering the reports on increased numerical abnormalities in spermatozoa and abnormalities of the meiotic chromosomes in infertile men with normal somatic karyotypes (for review, see De Braekeleer and Dao, 1991), a higher risk of paternally-derived aneuploidy cannot be excluded in ICSI pregnancies.

The identification of DNA polymorphism makes it possible to classify trisomy 21 according to parental origin and stage of the chromosomal error. If paternal heterozygosity was retained in the trisomic conceptus, we concluded an error at meiosis I during spermatogenesis. Non-disjunction at meiosis II or post-zygotic mitotic error would result in homozygosity. In the present report, the conceptus with trisomy 21 was a product of a normal oocyte and a disomic spermatozoon probably generated by a meiosis I error. Clearly, this report of a single case of paternally derived trisomy 21 does not prove that male derived aneuploidy has an increased frequency after ICSI.

For evaluating a possible male aneuploidy factor in infertile men, apart from meiotic studies of testicular biopsies (Egozcue et al., 1983), two approaches are feasible. Firstly, further studies on aneuploidy in spermatozoa of infertile men with normal somatic karyotype are needed. Secondly, it is important to determine the parent of origin in each case of aneuploidy. In order to assess the possible transmission of chromosomal abnormalities to the conceptus, the latter approach is more precise than estimating the incidence of aneuploid spermatozooa. Additional data from other centres are urgently needed to arrive at a firm estimate of the paternally derived aneuploidy risk after ICSI. We suggest offering prenatal diagnosis to all couples participating in an ICSI programme.

References

Received on February 23, 1998; accepted on October 1, 1998

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