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EDITORIAL

Incidence of chromosomal aberrations in children born after assisted reproduction through intracytoplasmic sperm injection

Intracytoplasmic sperm injection (ICSI) with spermatozoa from ejaculated sperm or, later on with epididymal or testicular spermatozoa, has been used in reproductive medicine since 1991. In 1995, In't Veld *et al.* reported a high incidence of sex-chromosomal aberrations in a small number of prenatal diagnostic tests, performed for maternal age. Our own results at that time as well as those from others were less striking, but there were grounds for concern (Liebaers *et al.*, 1995). At this point (i.e. up to August 1997), a total of 1082 prenatal tests had been performed in pregnancies after ICSI carried out in the Centre for Reproductive Medicine of the Brussels Free University Hospital: 690 amniocenteses, 15 of which were abnormal; 392 chorionic villus samplings (CVS), 13 of which were abnormal; and seven cord blood punctures, which were control samples for previous amniocenteses and were normal. Mean maternal ages were 32.7 years (± 4.06) for patients undergoing amniocentesis and 32.1 years (± 4.11) for patients undergoing CVS. In these 1082 tests we observed 18 (1.66%), de-novo chromosomal aberrations: nine of these (0.83%) were sex-chromosomal aberrations and another nine (0.83%) were autosomal aberrations (trisomies and structural) (Table I).

The figures in Table I show that there is a statistically significant increase in sex-chromosomal aberrations (0.83%), since the 95% confidence limit of this percentage (0.3–1.6%) does not contain the aberration percentage (0.19–0.23%) described in the literature with regard to a neonatal population (Nielsen and Wohlert, 1991; Jacobs *et al.*, 1992). The incidence of autosomal aberrations is due partly to the increase in trisomies, linked with higher maternal ages. On the other hand, there is also an increase in structural de-novo aberrations (0.36% compared with 0.07% in the literature) which is significant (Jacobs *et al.*, 1992). The increase in inherited structural aberrations (one of them being non-balanced) is, of course, higher than in the general population but was predictable for the individual couples, where the father was carrying the structural anomaly in all but one case.

An increased percentage of de-novo chromosomal aberrations may result from the ICSI procedure itself or it may be linked to a defined subgroup of males with impaired semen samples. It is interesting to observe that all de-novo sex-chromosomal aberrations were found after spermatozoa had been used from men with extreme oligoasthenoteratospermia (concentration 0.1–4.6×10^6/ml; normal morphology 0–40%; progressive motility 0–18%) (World Health Organization, 1992; Devroey, 1997). So far, however, we have not observed any correlation between the occurrence of chromosomal anomalies and standard semen parameters in the male partner (concentration, motility, morphology).

These data on karyotypes were obtained as a result of our group's decision, from the very introduction of this novel technique to organize a follow-up study of pregnancies and children (Bonduelle *et al.*, 1995b, 1996; Wisanto *et al.*, 1996). For the first 2 years, 85% of the counselled pregnant patients participated in the prenatal diagnosis programme. At that time we were still at an experimental stage of our ICSI programme and no data on prenatal karyotypes in ICSI were available besides our own. Patients had to agree to a prenatal diagnostic procedure as an entry criterion for the treatment. Now, however, we discuss our current risk figures and can offer a free choice as regards testing, taking into account the risk of miscarriage due to sampling (0.5–1%). Under these conditions, only 54.5% of the couples choose either CVS or amniocentesis. In this, patients also take into account that the increase in mainly sex-chromosomal aberrations is a more acceptable risk, since children with sex-chromosomal aneuploidies usually have a normal physical appearance and are likely to have IQs within the normal range of the population. Mental retardation, defined as IQ of <70, is not typically associated with sex chromosome aneuploidy. There is however a moderate risk of developmental problems in the areas of speech, motor skills and learning abilities. Moreover, infertility is often present (Linden *et al.*, 1997). The mean age of our ICSI patient population is 32.2 years and 49% of the patients aged <35 years decide to have a prenatal diagnosis, whereas 66% of those aged $\geqslant35$ years are prepared to do so.

Willingness to participate in the follow-up programme, however, is very encouraging, and we have complete information at birth for 98.2% of the children. We have been able to examine 84.5% of the children in our own department at the age of 2 months.

Since another group reported a much higher incidence of chromosomal anomalies after ICSI (In't Veld *et al.*, 1995; Van Opstal *et al.*, 1997) and many others have not clearly documented the karyotypes of the ICSI children born in their programme, we believe that there is a need for more information both from our own centre and from other centres, since inter-centre differences might exist. Collaborative efforts should draw attention to differences in results both in terms of pregnancy outcome and in numbers of karyotype anomalies or other adverse effects on the children (Bonduelle *et al.*, 1995a; Tarlatzis *et al.*, 1996). Furthermore, more information needs to be collected as to why such anomalies should occur. At this point, we think that patients should be informed and counselled before any treatment on the basis of the available data as to the higher risk of transmitted chromosomal aberrations, the risk of *de novo*, mainly sex-chromosomal aberrations and the risk of transmitting fertility problems to the offspring and that a free choice of prenatal diagnosis should be available in all ICSI settings (Chandley and Hargreave, 1996).

Table I. Karyotype anomalies in 1082 prenatal diagnoses

Abnormal karyotypes on 1082 prenatal tests	Maternal age (years)	Number	Percentage	95% confidence interval	Percentage in literature[a] (on 56 952 newborns)	Percentage in literature[b] (on 34 910 newborns)
De-novo chromosomal aberrations		18	1.66	1.0–2.7	0.445	
Sex-chromosomal:		9	0.83	0.3–1.6	0.19	0.23 (total sex-chromosomal)
45,X	37					
46,XX/47,XXX	44					
47,XXX (2 children)	32, 37					
47,XXY (4 children)	26, 28, 28, 32					
47,XYY	25					
Autosomal:		9	0.83	0.3–1.6	0.21	0.61 (total autosomal)
Trisomy 21 (5 children)	32, 33, 37, 41, 41	5	0.46		0.14	
structural		4	0.36		0.07	
46,XY,t(4;5)	30					
46,XX,t(2;15)	30					
46,XX,t(2;13)	36					
46,XX, inv(1qh)	39					
Inherited aberrations		10	0.92	0.4–1.7	0.47	
balanced		9	0.83		0.45	
unbalanced		1	0.09		0.023	
Total aberrations *de novo* + inherited		28	2.5	3.0–5.7	0.92	0.84

[a](Jacobs *et al.*, 1992).
[b](Nielsen and Wohlert, 1991).

Since we are also examining all children born after ICSI in a prospective study, we are able to report that 46 major malformations, i.e. those leading to functional impairment or necessitating surgery, have been observed in a total of, 1987 children at birth. This incidence of 2.3% is comparable to figures known from children born after in-vitro fertilization (IVF) (Bachelot *et al.*, 1995; Lancaster *et al.*, 1997), ICSI (Palermo *et al.*, 1996) or after natural conception (Lechat and Dolk, 1993) and is therefore reassuring, even though there is a need to collect data from other centres and from control groups, on the basis of a common approach to detecting births defects and using the same definitions (Kurinczuk and Bower, 1997). We think that here too, patients will be reassured on the basis of the available data.

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M.Bonduelle[1], A.Aytoz[2], E.Van Assche[1], P.Devroey[2], I.Liebaers[1] and A.Van Steirteghem[2]
[1]Centre for Medical Genetics and
[2]Centre for Reproductive Medicine, Medical Campus, Dutch-Speaking Brussels Free University, Laarbeeklaan 101, 1090-Brussels, Belgium