Obstetric outcome after prenatal diagnosis in pregnancies obtained after intracytoplasmic sperm injection

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In this study we compared the pregnancy outcome of 576 pregnancies after prenatal diagnosis with that of 540 pregnancies without prenatal diagnosis in our microinjection programme. Amniocentesis was suggested for singleton pregnancies (n = 465) and chorionic villus sampling (CVS) was proposed for twin pregnancies (n = 111 pregnancies, 222 fetuses). A total of 365 patients with singleton pregnancies and 175 patients with twin pregnancies who did not undergo prenatal diagnosis were selected as controls. Compared with the controls, the odds ratios in the amniocentesis group for preterm delivery, low birthweight, very low birthweight and fetal loss were 0.97 [95% confidence interval (CI): 0.60–1.57], 1.27 (95% CI: 0.78–2.06), 1.57 (95% CI: 0.53–4.66) and 0.86 (95% CI: 0.32–2.37) respectively. Compared with the controls, the odds ratios in the CVS group for preterm delivery, low birthweight, very low birthweight and fetal loss were 0.89 (95% CI: 0.61–1.30), 1.03 (95% CI: 0.74–1.45), 0.79 (95% CI: 0.41–1.53) and 0.47 (95% CI: 0.17–1.30) respectively. We concluded that, in this series of intracytoplasmic sperm injection (ICSI) pregnancies, prenatal testing did not increase the preterm-delivery, the low-birthweight, or the very low-birthweight rates as compared with those of the controls. In the prenatal diagnosis group, the fetal loss rate was comparable to that of the control group. Larger prospective controlled studies are needed in order to inform patients reliably about the risks and the advantages of prenatal testing in ICSI pregnancies.

Key words: amniocentesis/chorionic villus sampling/intracytoplasmic sperm injection/pregnancy outcome

Introduction

Mid-trimester amniocentesis and first-trimester chorionic villus sampling (CVS) are now offered routinely to women at increased risk of having a child with a chromosomal abnormality, particularly to women over the age of 35. Since its introduction in 1991, the safety of intracytoplasmic sperm injection (ICSI) has been of particular interest. Consequently, a prospective follow-up study of pregnancies and children was carried out in our centre, including agreement to genetic counselling and prenatal diagnosis, and physical examination of the children born after ICSI (Bonduelle et al., 1996). As part of the study, all patients were asked to undergo a prenatal diagnosis if they became pregnant. The question has been raised as to whether prenatal testing involves additional risks for the patients undergoing ICSI. In this study, we report on our experience with prenatal diagnostic techniques, i.e. mid-trimester amniocentesis for singleton pregnancies and first-trimester CVS for twin pregnancies after ICSI.

Materials and methods

The obstetric outcomes of 576 ICSI pregnancies after prenatal diagnosis were compared with the obstetric outcomes of 540 ICSI pregnancies without prenatal diagnosis at similar ages and parity. Obstetric outcomes of 904 pregnancies and prospective follow-up study of 877 children born after ICSI have been reported previously (Bonduelle et al., 1996; Wisanto et al., 1996). As part of the follow-up study, all patients were asked to undergo a prenatal diagnosis. The risks and benefits of the different types of prenatal diagnosis were discussed in detail at ~6 to 8 weeks of gestation. In our ICSI programme, 54.5% of couples agreed to undergo prenatal diagnosis. The main reason for not agreeing to prenatal diagnosis was fear of losing the pregnancy; a smaller group refused because of religious reasons. All ICSI patients had an ultrasound examination at the 7th week of gestation. The patients who agreed to prenatal testing had a second detailed structural ultrasound examination prior to the diagnostic procedure. Amniocentesis was suggested for singleton pregnancies and CVS was proposed for multiple pregnancies (De Catte et al., 1996). The prenatal diagnosis was performed mainly by two experienced operators.

Before amniocentesis, the abdomen was disinfected with a polyvidone chloride solution. Amniocentesis was carried out transabdominally under ultrasound guidance using a 22 G spinal needle. A sample of 20 ml of amniotic fluid was removed from the amniotic cavity. A sample of 18 ml of amniotic fluid was sent to the cytogenetics laboratory for long-term culture and 2 ml was used to determine the concentration of α-fetoprotein. Chromosome preparations were obtained from cultured amniocytes according to a modified technique by Verma and Babu (1989).

The technique of CVS has been described previously (De Catte et al., 1996). CVS was performed under ultrasound guidance (Toshiba, SSA 250, SSA 270, curved linear probe, 3.75 and 5 MHz). Detailed sonography prior to the chorion sampling was used to identify the placental localization and its chorionicity, to clearly map all fetuses and placentas, and to discuss the technical approach for each fetus individually. Chorionic villi were aspirated transcrinally by a Portex catheter or transabdominally, using a double-needle system (outer needle 18G, inner needle 20G). Short- and long-term chromosomal
Preterm delivery (<37 weeks), low birthweight (<2500 g), very low birthweight (<1500 g) and total pregnancy loss as compared with those of a control group. Patients who had two consecutive prenatal tests in order to confirm previous karyotyping or who had selective feticide for triplet or quadruplet pregnancies were not included in the study.

The χ² test or Fisher’s exact probability test was used to compare the percentages in different groups and the independent risk effect from different prenatal diagnosis techniques was analysed using odds ratios computed with 95% confidence intervals (CI) (Medcalc, Medcalc Software, Ghent, Belgium).

### Results

Amniocentesis was performed in 465 singleton ICSI pregnancies at a mean gestational age of 15.8 weeks (range 14–18). The mean maternal age was 32.9 years (range 22–45). The mean maternal age in the control group was 31.84 years (range 19–43). Chorionic villus biopsy was performed in 111 twin ICSI pregnancies at a mean gestational age of 11.1 weeks (range 11–14). The mean maternal age was 31.98 years (range 23–40) in the study group and 31.46 years (range 23–40) in the control group. The cytotogenic results of 222 CVS samples and 465 amniotic fluid samples are shown in Table I. The mean numbers (± SD) of needle insertions in the CVS group for the first and second fetuses were 1.1 ± 0.3 and 1.1 ± 0.2, respectively. In one case the karyotype of one fetus was misdiagnosed after CVS. There were 343 males and 318 females with normal karyotypes. Six of 687 samples were not suitable for cytogenetic analysis. The results from seven prenatal diagnosis procedures performed in other centres could not be obtained (Table II). Thirteen out of 674 samples available for analysis were abnormal (1.93%). Of these seven were de novo (four sex-chromosomal aberrations and two reciprocal translocations) and six were inherited chromosomal aberrations (one reciprocal, one Robertsonian, two inversions and two supernumerary) as listed in Table II.

In the amniocentesis group, five pregnancies including four terminations (two for abnormal karyotypes, two for congenital malformations detected by ultrasound examination) ended before 20 weeks gestation, and five pregnancies were lost after 20 weeks of gestation. The total post-procedural loss rate, including one spontaneous abortion (loss before 20 weeks) and five stillbirths (loss at 20 weeks or later), was 1.30% (6/461). In the control group, 10 out of 365 pregnancies were lost (2.74%) beyond 15.5 weeks of gestation, which was the mean intervention date for amniocentesis. Five pregnancies were lost spontaneously before 20 weeks. Five fetuses died after 20 weeks gestation. The total pregnancy-loss rates were not statistically different between the two groups ($P = 0.22$) (Table III). In patients <35 years, the pregnancy-loss rates were 1.69% (5/295) and 2.92% (8/274) in the amniocentesis and in the control groups respectively (not significant; χ² test), while in patients ≥35 years the pregnancy-loss rates in the study group and in the controls were 0.60% (1/166) and 2.20% (2/91) respectively (not significant; Fisher exact test).

A total of 460 pregnancies after amniocentesis were evaluated beyond 20 weeks of gestation. Forty-one of these 460 pregnancies ended before 37 weeks gestation (8.91%). There were 46 infants (10.00%) weighing <2500 g and 10 infants (2.17%) weighing <1500 g at birth. In the control group, 360 pregnancies were evaluated beyond 20 weeks gestation. The prematurity, low-birthweight and very low-birthweight rates were 9.17%, 8.06% and 1.39% respectively (Table IV). The risk of having preterm delivery, low birthweight and very low-birthweight did not increase after amniocentesis. Compared with pregnancies without prenatal diagnosis, the odds ratios for preterm delivery, low birthweight and very low-birthweight were 0.97 (95% CI: 0.60–1.57), 1.27 (95% CI: 0.78–2.06) and 1.58 (95% CI: 0.53–4.66) respectively, in the amniocentesis group.

A total of 222 chorionic villus samples were analysed in 111 twin pregnancies. One twin pregnancy was reduced to a singleton because of the presence of trisomy 21 in one of the fetuses. There were six spontaneous losses (2.71%) among women who underwent CVS and 11 losses (3.14%) in the controls. This difference was not significant ($P = 0.97$) (Table III). In the CVS group, the pregnancy-loss rate was 3.07% (5/163), where maternal age was younger than 35 years, and it was 1.72% (1/58), where maternal age was ≥35 years. In the control group, the pregnancy-loss rate was 3.68% (10/272), where the mothers were younger than 35 years, and it was 1.28% (1/78) where they were ≥35 years. The pregnancy-
loss rates in the controls and in the CVS group were similar in the different age groups.

Pregnancy outcome in the CVS group (Table IV) was studied in 109 twin pregnancies or 217 fetuses beyond 20 weeks gestation. Fifty-eight pregnancies delivered preterm (53.21%). The low-birthweight (n = 114) and the very low-birthweight (n = 14) rates were 52.53% and 6.45%, respectively. In the control group, 174 twin pregnancies or 348 fetuses were followed beyond 20 weeks gestation. Preterm deliveries occurred in 101 pregnancies (58.05%). The low-birthweight (n = 180) rate and the very low-birthweight (n = 28) rate were 51.72% and 8.05% respectively. Compared with pregnancies without prenatal diagnosis, the odds ratios for prematurity, low-birthweight and very low-birthweight were 0.89 (95% CI: 0.61–1.30), 1.03 (95% CI: 0.74–1.45) and 0.79 (95% CI: 0.41–1.53) respectively in the CVS group (Table IV).

**Discussion**

There have been few studies to assess spontaneous abortion rates after normal first-trimester ultrasound examination in the general population (Gustavii, 1984; Wilson et al., 1984). Such studies have reported a pregnancy-loss rate varying from 2.13% (±20 weeks gestation) to 7.2% (±28 weeks gestation) after a normal ultrasound examination at the 10th week of gestation. Gustavii (1984) also reported that the spontaneous-abortion rate was 2.3% (±28 weeks gestation) after a normal ultrasound examination at the 14th week of gestation. In another study where only patients with threatened abortion were evaluated, a 12% pregnancy loss rate has been reported (Mantoni and Pedersen, 1982). We believe that these figures are very important in estimating the added risk of spontaneous abortion after prenatal diagnosis. So far there have been no published data assessing pregnancy losses after ICSI. In the amniocentesis group in our series the pregnancy-loss rate, including spontaneous abortions and stillbirths, was 1.30%. In the CVS group, the pregnancy-loss rate was 2.71% in twin pregnancies. These results are compatible with the previously reported loss rates in the general population (Gustavii, 1984; Wilson et al., 1984).

In our group of ICSI pregnancies, the pregnancy-loss rate after amniocentesis (1.30%) was also comparable to that of our control group (2.74%) in singleton pregnancies. In the control group, five spontaneous abortions occurred, while in the amniocentesis group there was only one spontaneous abortion. Terminations following the diagnosis of a cytogenetic abnormality might have removed some cases from the study group which would have aborted spontaneously. Because of lack of ultrasound examination in the control group at the corresponding date of amniocentesis, dead fetuses might have been included in the control group. The spontaneous-abortion rate in the control group might therefore have been overestimated. In the literature, two case-controlled studies have reported similar pregnancy-loss rates after amniocentesis and in control groups (NICHD, 1976; MRC, 1978). The only randomized case-controlled study including women younger than 35 years without genetic risk has shown that, in the amniocentesis group, the spontaneous-abortion rate (from 16 to 28 weeks gestation) (1.7%) was significantly higher than that in the control group (0.7%) (Tabor et al., 1986). In this
study, the intervention was performed by five clinicians with different experience and with an 18-gauge needle. In our study group, two experienced operators performed the amniocenteses with a 22-gauge needle. In this series of ICSI pregnancies, amniocentesis did not emerge as a risk factor for prematurity, low-birthweight or very low-birthweight as compared with that in controls. Tabor et al. have also reported similar preterm-delivery rates after amniocentesis and in control groups (Tabor et al., 1986). However, in ICSI pregnancies the preterm-delivery rate, the low-birthweight rate and the very low-birthweight rate remain higher than in the general population (Bekaert et al., 1997).

It has been reported that selective feticide of an abnormal twin fetus in the second trimester increases the morbidity and the mortality of the normal twin (Evans et al., 1994). In our practice, CVS is proposed for twin ICSI pregnancies because of the advantage it has of providing an earlier diagnosis than amniocentesis. Thus, a selective feticide can be carried out at an earlier gestational age. In the study, the fetal-loss rate after CVS (2.71%) was comparable to the pregnancy-loss rate in controls (3.14%). In the CVS group, four pregnancies (eight fetuses) were lost up to 20 weeks after chorionic villus biopsy. The earliest loss was 5 weeks after the procedure. The loss rate in our study population is in line with that in the study published by De Catte et al. (1996) which evaluated the pregnancy outcome after CVS in twin pregnancies. Large-scale studies have confirmed the safety of CVS, finding no statistically significant difference in fetal-loss rates as compared with those of controls undergoing second-trimester amniocentesis (Canadian Collaborative CVS-Amniocentesis Clinical Trial Group, 1989; Rhoads et al., 1989).

In our twin pregnancies, the preterm-delivery rate, the low-birthweight rate and the very low-birthweight rate after CVS were comparable to those of the controls who did not undergo prenatal testing. Similar results have been reported previously (De Catte et al., 1996).

It is well known that the rate of aneuploidy increases with maternal age (Hook et al., 1984). Prenatal diagnosis is therefore of the utmost importance for women over 35 years. Questions still remain as to whether prenatal diagnosis is needed for women younger than 35 and whether prenatal diagnosis involves additional risks for such patients undergoing ICSI. We evaluated our data in this respect for two different age groups, i.e. ≥35 and <35 years. In women younger than 35 years, the pregnancy-loss rates after CVS and amniocentesis were comparable to the pregnancy-loss rates in women of the same age who did not undergo prenatal diagnosis.

An earlier prospective follow-up study of 877 children born after ICSI has shown a slight increase in de-novo chromosomal aberrations (1.2%) and a higher frequency of transmitted chromosomal aberrations (Bonduelle et al., 1996). This present study evaluating pregnancy outcome after ICSI shows that, compared with those of the controls, the pregnancy-loss rate, the preterm-delivery rate, the low-birthweight rate and the very low-birthweight rate did not increase in the prenatal-diagnosis groups. We believe that the safety of microinjection treatment should be confirmed by collaborative studies. In the meantime, and as part of counselling, prenatal diagnosis should be offered to all patients undergoing ICSI.

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