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Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks' gestation

Kypros Nicolaides, Maria de Lourdes Brizot, Fatima Patel, Rosalinde Snijders

Summary

We did a prospective study of women with singleton viable pregnancies at 10–13 weeks' gestation who requested first-trimester fetal karyotyping because of advanced maternal age, parental anxiety, or family history of chromosomal abnormality.

Women were counselled as to the available options of non-invasive screening or invasive testing by mid-trimester amniocentesis, early amniocentesis (EA), or chorionic villus sampling (CVS), or randomisation to EA or CVS at 10–13 weeks. EA was done in 731 patients (493 by choice and 238 by randomisation) and CVS in 570 (320 by choice and 250 by randomisation). Both procedures were done by transabdominal ultrasound-guided insertion of a 20-gauge needle. The rate of successful sampling was the same for both procedures (97·5%).

Spontaneous loss (intrauterine or neonatal death) was significantly higher after EA (total group mean = 5·3%, 95% CI 3·8–7·2; randomised subgroup mean = 5·9%, 3·3–9·7) than after CVS (total group: mean = 2·3%, 1·2–3·9; randomised subgroup: mean = 1·2%, 0·3–3·5). The gestation at delivery and birthweight of the infants after EA and CVS were similar. In the EA group the incidence of talipes equinovarus (1·63%), was higher than in the CVS group (0·56%), but this difference was not significant.

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Introduction

Amniocentesis for fetal karyotyping is traditionally done during the second trimester at 16 weeks' gestation. A randomised study reported that this technique is associated with a 1% risk of spontaneous abortion.[1] In the early 1980s first-trimester diagnosis became possible with the introduction of chorionic villus sampling (CVS). Three randomised trials comparing the safety of first-trimester CVS and second-trimester amniocentesis reported conflicting results; the chance of having a successful pregnancy outcome after first-trimester CVS was 4·6% lower,[2] 0·6% lower,[3] or 0·1% higher.[4] In these studies, the need for repeat testing after CVS, because of inadequate sample, mosaic result, or culture failure, was 3–10%.

In the late 1980s, early amniocentesis (EA) was introduced and four studies with complete pregnancy follow-up have reported that the procedure-related rate of fetal loss was 3·3–6·6%.[5-8] We compared the safety of EA and CVS done at 10–13 weeks' gestation.

Patients and methods

From January, 1990, women referred to our centre requesting first-trimester fetal karyotyping were counselled as to the available options for non-invasive screening and invasive testing. Non-invasive screening included maternal blood testing at 16 weeks' gestation and ultrasound examination at 20 weeks' for fetal defects.[9,10] If the results of these tests suggested that the risk was increased, amniocentesis or cordocentesis would be offered. From September, 1992, non-invasive screening included ultrasound examination at 10–13 weeks' for measurement of fetal nuchal translucency thickness; if the thickness was 3 mm or greater,[11] first trimester double-needle CVS would be done to ensure sufficient tissue was obtained for direct preparation in addition to long-term culture.

The options for invasive testing were late amniocentesis (at 15–18 weeks'), EA (at 10–13 weeks'), and CVS (at 10–13 weeks').

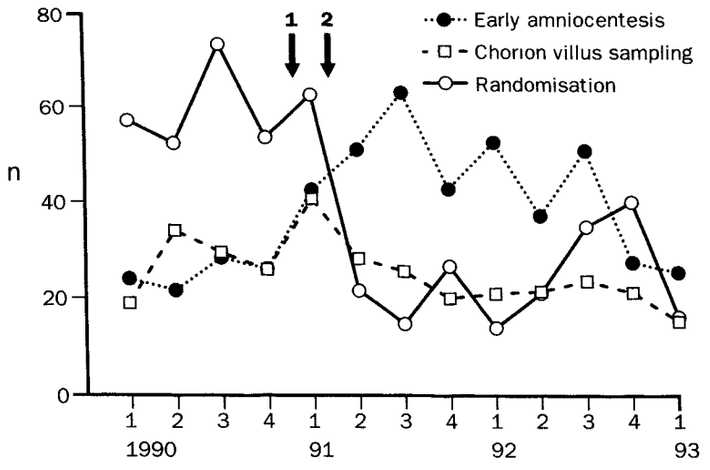

Figure 1: **The choices of women requesting first-trimester fetal karyotyping between 1990 and 1993**

Arrows show publication of reports that CVS can cause limb abnormalities[13] (1) and is associated with a much higher risk of spontaneous abortion than amniocentesis (2).[2]

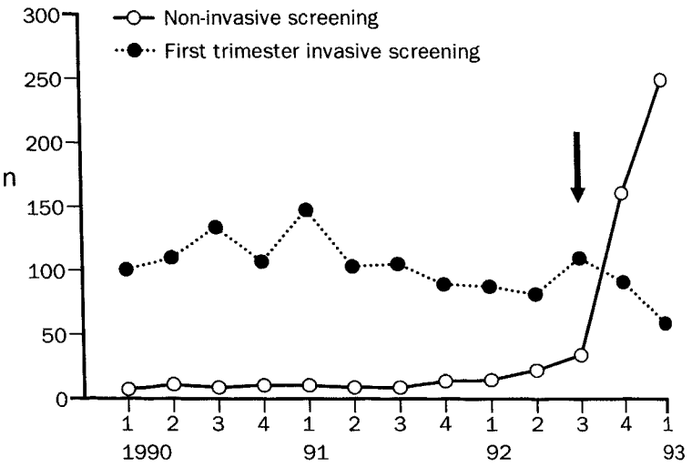

Figure 2: **Non-invasive screening and first-trimester invasive testing**

Arrow shows publication of a study suggesting that first-trimester ultrasonography for measurement of fetal nuchal translucency thickness is an effective non-invasive method of screening for fetal trisomies.[11]

Patients were told that all procedures are done in a similar fashion, the procedure-related risk of fetal loss from late amniocentesis and CVS was similar (approximately 1%),[1,4] and that EA was a new technique and we were uncertain if the risk was less or more than that of CVS. We also explained that in about 3% of cases there was a need to repeat the test either because of failure to get a result or because the result was inconclusive. Patients were offered a choice of randomisation into EA or CVS (the mother selected one of two sealed, opaque envelopes that contained a card for one of the procedures).

Written informed consent was obtained from patients for the study, which was approved by the ethical committee of our hospital.

In a pilot study we found that at less than 10 weeks' gestation there was a high rate of failure to culture amniotic fluid.[12] Furthermore, in our experience with CVS for fetal karyotyping during 1984–1989 the fetal loss rate was much higher when the procedure was done before 10 weeks' (7·4% of 202 cases at 8–9 weeks', 3·2% of 1084 cases at 10–11 weeks' and 1·9% of 257 cases at 12–13 weeks').

Criteria for inclusion were the women's request for first-trimester fetal karyotyping because of advanced maternal age, parental anxiety, or family history of chromosomal abnormality in the absence of parental chromosomal rearrangement, and ultrasonographic evidence of singleton pregnancy at 10 to 13 weeks' gestation and viable fetus with a minimum crown-rump length of 38 mm. We excluded those patients in whom ultrasound examination showed increased fetal nuchal translucency thickness (in these cases double-needle CVS was preferred), missed abortion, multiple pregnancy, major fetal abnormality, intrauterine contraceptive device in situ, or multiple fibroids or large areas of placental haemorrhage making either procedure impossible or one of the procedures technically easier.

All procedures were carried out in the Harris Birthright Research Centre for Fetal Medicine by a specialist in fetal medicine or under his direct supervision by any one of 16 research registrars. Both procedures were done by transabdominal ultrasound-guided insertion of 20 gauge needle by a free-hand technique. The maternal bladder was empty and no local anaesthesia was used. No prophylactic antibiotics were given and the patients were advised that rest after the procedure was unnecessary.

At EA puncture of the placenta was avoided and 11 mL of fluid aspirated (the first 1 mL was discarded to avoid contamination with maternal tissues). For CVS, the tip of the needle was moved 5–10 times within the substance of the placenta while negative pressure was applied by manual aspiration (6–10 mL) through a 20 mL syringe that was attached to the hub of the needle; care was taken to avoid puncture of the amniotic membrane.

The samples were sent to one of two laboratories (Dr Rodney Meredith of Cytogenetic Services, London, UK, and Karen Marks

	Total n = 1301	EA		CVS	
		Choice n = 493	Randomised n = 238	Choice n = 320	Randomised n = 250
Mother					
Median age (range) in yr	38 (22–46)	38 (23–45)	38 (24–45)	38 (22–46)	38 (22–46)
Employed (%)	856 (65 8)	325 (65 9)	165 (69 3)	198 (61 9)	168 (67 2)
Current smoker (%)	114 (8 8)	43 (8 7)	19 (8 0)	30 (9 4)	22 (8 8)
Median weight (range)	61 (41–117)	61 (43–117)	60 (41–92)	60 (43–116)	60 (44–96)
< 50 kg (%)	70 (5 4)	24 (4 9)	13 (5 5)	19 (5 9)	14 (5 6)
> 80 kg (%)	46 (3 5)	22 (4 5)	7 (2 9)	11 (3 4)	6 (2 4)
Vaginal bleeding					
Any (%)	281 (21 6)	101 (20 4)	51 (21 4)	68 (21 3)	61 (24 4)
Heavy (%)	41 (3 2)	14 (2 8)	9 (3 8)	8 (2 5)	10 (4 0)
Obstetric history					
First pregnancy (%)	231 (17 8)	86 (17 4)	38 (16 0)	61 (19 1)	46 (18 4)
Previous perinatal death (%)	377 (29 0)	152 (30 8)	76 (31 9)	83 (25 9)	66 (26 4)
Previous live birth (%)	942 (72 4)	369 (74 9)	162 (68 1)	230 (71 9)	181 (72 4)
Previous termination of pregnancy (%)	295 (22 7)	110 (22 3)	63 (26 5)	66 (20 6)	50 (20 0)
Fetus					
Median gestation (range)	11 (10–13)	11 (10–13)	11 (10–13)	11 (10–13)	11 (10–13)
Median crown-rump length (range)	52 (38–92)	52 (38–92)	51 (38–86)	51 (38–91)	52 (38–89)
Placenta					
Anterior	706 (54 3)	268 (54 4)	114 (47 9)	183 (57 2)	141 (56 4)

Table 1: **Maternal characteristics and ultrasound findings**

Karyotype	EA		CVS	
	Choice	Randomised	Choice	Randomised
Normal				
Female	234 (47 5%)	119 (50 0%)	151 (47 1%)	124 (49 6%)
Male	247 (50 1%)	114 (47 9%)	156 (48 8%)	118 (47 2%)
Mosaicism confined	1 (0·1%)		2 (0 1%)	2 (0 8%)
Trisomy				1
Sex chromosome aneuploidy			2	1
Polyploidy	1			
Unbalanced abnormalities	11 (2 2%)	5 (2 1%)	17 (3 0%)	6 (2 4%)
Autosomal trisomy				
Trisomy 21	6	4	5	2
Trisomy 18	1	1	3	
Trisomy 13				2
Other	2			1
Sex chromosome aneuploidy				
47, XXX	1			
47, XXY	1		1	
Mosaicism true				
Trisomy			1	1
Sex chromosome aneuploidy			1	
Total	493	238	320	250

Table 2: **Cytogenetic results**

of University Diagnostics Limited, London, UK) and cytogenetic analysis was done after long-term culture.

Demographic details, previous pregnancy history, menstrual cycle, last menstrual period, any vaginal bleeding since conception (spotting or heavy), maternal weight, ultrasound findings (fetal crown-rump length, and placental site anterior or posterior), and the procedure performed were recorded. Pregnancy outcome was obtained from the mothers or the referring obstetricians or general practitioners. At the time of testing, the mother was given an outcome form requesting basic information on gestation and mode of delivery, sex and birthweight of the infant, and any obvious abnormality. If this form was not received within 4 weeks after the expected date of delivery a telephone inquiry was made and new forms were sent to the mothers and their doctors.

The rates of fetal loss (total, induced, and spontaneous) in the CVS and EA groups (both in those that were randomised and in those who chose a procedure) were calculated with 95% confidence intervals (CI). χ^2 test was used to examine significance of differences between the various groups.

It was assumed that the total fetal loss rate (termination of pregnancy, spontaneous abortion, intrauterine or neonatal death) after CVS or EA would be about 7%[3] and 5%, respectively. To show that this assumed difference was significant (test of significance at the 5% level, power 80%) it was estimated that 4400 patients would need to be recruited to the study. However, by March, 1993, recruitment to the study was collapsing (figure 1), presumably because of the widespread publicity that CVS can cause fetal limb abnormalities[13] and is associated with a high risk of spontaneous abortion,[2] and that non-invasive screening by ultrasonography[10,11] and maternal serum biochemistry[9] can provide sufficient reassurance to avoid invasive testing.

Results

From January, 1990, to March, 1993, 2094 women were recruited. 224 patients were excluded because ultrasound examination showed an anembryonic pregnancy or dead fetus (96), multiple pregnancy (65), major fetal abnormality (1 with anencephaly, 2 with exomphalos, and 1 with amnion dysruption sequence), intrauterine contraceptive device in-situ (2), multiple fibroids or large areas of placental haemorrhage (19), or increased fetal nuchal translucency thickness (38).

The choices of the remaining 1870 women were non-invasive screening (534), second-trimester amniocentesis (35), EA (493), CVS (320), and randomisation (488); 250 were randomised to CVS and 238 to EA. Figures 1 and 2 show how patients' choices changed during the study period. The CVS and EA groups (both women who were randomised and who chose one of the procedures) were similar with respect to maternal age and weight, employment, cigarette smoking, previous obstetric history, vaginal bleeding, gestation at sampling, fetal crown-rump-length, and placental site (table 1).

In all cases, the allocated procedure was done. Amniotic fluid was successfully obtained at the first attempt in 718 patients (98·2%) and at the second in 13 (1·8%); there were no instances of obvious blood contamination. CVS provided sufficient material for cytogenetic analysis in 566 of the 570 cases, in 549 cases (96·3%) at the first attempt and in 17 (3·0%) after two needle insertions; in 4 cases (0·7%) the samples obtained at the first attempt were thought to be sufficient but subsequent examination in the laboratory showed maternal tissue only.

There was no significant difference in sex distribution or frequency of abnormal karyotype between randomised subgroups of EA and CVS (table 2). In the EA group (731) cell culture provided a non-mosaic cytogenetic result in 713 (97·5%); in 17 (2·3%) there was culture failure, and in 1 (0·1%) there was a mosaic result. In the CVS group (566, excluding the 4 where only maternal tissue was obtained), cell culture provided a non-mosaic cytogenetic result in 556 (98·2%); in 3 (0·5%) there was culture failure, and in 7 (1·2%) a mosaic result.

The need for repeat testing was the same for both EA and CVS (2·5%). However, the main indication for repeat testing in the CVS group was mosaicism (1·2% compared with 0·1% for EA, $p < 0·05$), whereas in the EA group it was failed culture (2·32 *vs* 0·53% for CVS, $p < 0·01$). The rate of culture failure in the EA group was related to gestation at sampling (8 of 152 [5·26%] at 10 weeks, 7 of 329 [2·12%] at

Outcome	Total n = 1301		EA				CVS				χ^2	
			Choice n = 493		Randomised n = 238		Choice n = 320		Randomised n = 250			
	n	%	n	%	n	%	n	%	n	%	Choice	Randomised
Survival	1211	93 1	45	92 7	21	91 6	298	93 1	23	95 2		
Not known	1	6 8	7	7 1	8	8 4	22	6 9	8	4 8	0 07	2 03
Total loss	89	4 0	35	5 1	20	5 9	10	3 1	12	1 2	1 24	6 51
Spontaneous death	52	2 8	25	2 0	14	2 5	12	3 8	3	3 6		
Termination	37	2 4	10	1 8	6	2 1	11	3 4	9	2 4		
Chromosomal defect	31	0 5	9	0 2	5	0 4	1	0 3	6	1 2		
Normal karyotype	6	0 1	1	0 2	1				3			
No follow-up	1		1									

Table 3: **Pregnancy outcome**

	EA		CVS	
	Choice n=25	Randomised n=14	Choice n=10	Randomised n=3
Interval				
0–2 wk	9 (36%)	7 (50%)	3 (23%)	1 (33%)
3–4 wk	6 (24%)	1 (7%)	6 (46%)	2 (67%)
5–8 wk	5 (20%)	1 (7%)	1 (8%)	
9–12 wk	3 (12%)		1 (8%)	
13–30 wk	2 (8%)	5 (36%)	2 (15%)	
Gestation				
<24 wk	23 (92%)	9 (64%)	11 (84%)	3 (100%)
24–28 wk		1 (7%)	1 (8%)	
>28 wk	2 (8%)	4 (29%)	1 (8%)	

Table 4: **Interval between sampling and spontaneous loss and gestation at loss**

11 weeks, 2 of 167 [1·19%] at 12 weeks, and 0 of 82 at 13 weeks).

There were 32 cases with inconclusive or no results, 18 from the EA group and 14 from the CVS group, including the 4 where only decidual tissue was obtained. Of these 32 cases, 16 subsequently had CV, 8 had amniocentesis, 4 had cordocentesis, and 4 declined further invasive testing. In 28 of these 32 patients, healthy infants were delivered and in 4 cases the pregnancy was terminated after repeat testing showed chromosomal abnormalities.

Outcome information was obtained for all but 1 pregnancy. There were 89 deaths and 1211 survivors. In 52 cases the deaths were spontaneous and in 37 cases the pregnancies were terminated at the request of the parents. Terminations were done for fetal chromosomal abnormalities (31), other abnormalities diagnosed by ultrasonography after invasive testing (2 neural tube defects and 1 infantile polycystic kidney disease, all from the randomised CVS group), and 3 for other reasons (the karyotype was male in 2 and female in 1).

The rates of survival and total loss (spontaneous and induced) were not significantly different for CVS and EA (table 3). However, spontaneous loss (intrauterine or neonatal death) in the randomised group was significantly higher after EA (mean = 5·9%, 95% CI 3·3–9·7) than after CVS (mean = 1·2%, 95% CI 0·3–3·5). The excess spontaneous loss after EA compared CVS was 3·0% 1·0–5·1) for the total groups and 4·7% (1·4–8·0) for the randomised subgroups.

Pregnancies resulting in losses and survivors were compared for maternal factors, obstetric history, vaginal bleeding before sampling, gestation and fetal crown-rump-length at sampling, and position of the placenta. χ^2 analysis showed that the only significant difference from the overall group was a higher rate of heavy vaginal bleeding before sampling in the group with fetal loss ($p < 0·01$) (data not shown). The intervals between sampling and spontaneous loss are shown in table 4. In the EA group the highest rate of pregnancy loss was within 2 weeks of sampling whereas in the CVS group it was 3–4 weeks after the procedure.

In livebirths, the mean gestation at delivery, the frequency of preterm birth, the mean birthweight, and the frequency of growth retardation (birthweight below the 10th centile of the normal range for gestation)[14] were not significantly different between the EA and CVS groups. Congenital defects were reported in 23 of 675 (3·4%) survivors in the EA group and 15 of 536 (2·8%) in the CVS group (table 5). In addition, in the CVS group there were 3 terminations of pregnancy for major defects in chromosomally normal fetuses that were diagnosed antenatally.

Defect	EA		CVS	
	Choice	Randomised	Choice	Randomised
Cleft lip and palate	1		1	1
Ventricular septal defect		1		
Pulmonary stenosis		1		
Diaphragmatic hernia		1		
Cutaneous haemangioma	1			1
Unilateral renal defect		1	1	
Hydrocoele	1	1	2	1
Syndactyly		1		2
Polydactyly	1			
Overlapping toes	1		1	
Shortened toes	1		1	
Talipes equinovarus	7	4	2	1
Total	13/457 (2 8%)	10/218 (4 6%)	8/298 (2 7%)	7/238 (2 9%)

In addition in CVS group 3 chromosomally normal fetusus were diagnosed to have major defects and the pregnancies were terminated.

Table 5: **Congenital defects**

Discussion

This prospective study compared two techniques for fetal karyotyping in the first trimester of pregnancy. Women requesting prenatal diagnosis are inevitably influenced by the widespread publicity on new methods of screening for fetal chromosomal abnormalities and the risks associated with the various techniques of invasive testing. In this study, women were given the option to choose between the available methods of non-invasive screening and invasive testing, and in the analysis of data we made comparisons within the group that was randomised and among women who chose to have EA or CVS.

EA and CVS were done for the same indication, at the same gestational range, by the same group of operators, by essentially the same technique of transabdominal ultrasound-guided insertion of a 20 gauge needle, and the samples were sent to the same laboratories. Therefore, the results are likely to reflect the inherent risk and efficacy of sampling the different tissues and not operator variability. In the multicentre Canadian, European, and Danish trials,[2-4] comparing first-trimester CVS with second-trimester amniocentesis, there were varying degrees of experience in obtaining and processing samples and different sampling techniques, including a wide range in gestation for transabdominal or transcervical aspiration, biopsy forceps, or needles of variable size, which may have contributed to the conflicting results.[2-4]

Our results suggest that EA is an alternative to CVS for first-trimester fetal karyotyping. Amniotic fluid was successfully obtained from all women requesting or allocated to this procedure and in 98·2% of the cases the sample was obtained after only one needle insertion. This success rate is the same as for second-trimester amniocentesis,[1] despite the fact that in the first trimester the amniotic cavity is much smaller and the placenta proportionately more extensive. CVS provided sufficient material for cytogenetic analysis after one needle insertion in 96·3% of the cases, which compares favourably with the 68% rate reported in the European trial.[2]

Gestation at delivery and birthweight of the infants after EA and CVS were similar and the frequencies of preterm delivery or low birthweight were no higher than would be expected in a normal population.[14] The frequency of congenital malformations after CVS and EA in our study was similar to that reported after CVS and second-trimester

amniocentesis in the European and Danish studies; the Canadian study did not provide any such data.[2-4] There were no cases of the oromandibular-limb hypogenesis syndrome; however, in 2 cases of the CVS group and 1 of the EA group there was shortening of some of the toes in one of the feet. The incidence of talipes equinovarus (1·63%), was higher in the EA group than in the CV group (0·56%), but this difference was not significant. A previous randomised study of second-trimester amniocentesis has shown that the incidence of talipes (0·8%) was not significantly different from controls that did not have invasive testing.[1]

Our data suggest that EA and CVS, done in a fetal medicine centre with experience in transabdominal ultrasound-guided techniques, are equally effective in providing conclusive cytogenetic results. On the basis of these findings it might appear that EA rather than CVS is likely to become the established first-trimester technique for fetal karyotyping. The widespread experience with second-trimester amniocentesis can be more easily adapted to do EA rather than CVS. EA has the additional advantage over CVS that the processing of samples requires less experienced laboratory staff, can be done in batches, and is less labour intensive. However, it is more likely that CVS will become the established technique because EA may be associated with 2–3% excess risk of fetal loss and possibly a higher incidence of talipes among survivors.

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