Ultrasound Obstet Gynecol 2009; **34**: 19–24
Published online 5 June 2009 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.6377

Fetal loss rate after chorionic villus sampling and amniocentesis: an 11-year national registry study

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KEYWORDS: amniocentesis; CVS; fetal loss; prenatal diagnosis

ABSTRACT

Objective *To assess the fetal loss rate following amniocentesis and chorionic villus sampling (CVS).*

Methods *This was a national registry-based cohort study, including all singleton pregnant women who had an amniocentesis (n = 32 852) or CVS (n = 31 355) in Denmark between 1996 and 2006. Personal registration numbers of women having had an amniocentesis or a CVS were retrieved from the Danish Central Cytogenetic Registry, and cross-linked with the National Registry of Patients to determine the outcome of each pregnancy. Postprocedural fetal loss rate was defined as miscarriage or intrauterine demise before 24 weeks of gestation.*

Results *The miscarriage rates were 1.4% (95% CI, 1.3–1.5) after amniocentesis and 1.9% (95% CI, 1.7–2.0) after CVS. The postprocedural loss rate for both procedures did not change during the 11-year study period, and was not correlated with maternal age. The number of procedures a department performed had a significant effect on the risk of miscarriage. In departments performing fewer than 500 amniocenteses, the odds ratio for fetal loss was 2.2 (95% CI, 1.6–3.1) when compared to departments performing more than 1500 procedures during the 11-year period. For CVS the risk of miscarriage was 40% greater in departments performing 500–1000 and 1001–1500 as compared to those performing more than 1500 procedures.*

Conclusions *The miscarriage rates (i.e. spontaneous loss and procedure-related loss) after amniocentesis and CVS were 1.4% and 1.9%, respectively. This difference may be explained by the difference in gestational age at the time of the procedures. The miscarriage rate was inversely correlated with the number of procedures performed in a department. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The risk of miscarriage following genetic amniocentesis and chorionic villus sampling (CVS) was investigated in randomized clinical trials in the 1980s and early 1990s[1–5]. A study evaluating amniocentesis vs. no invasive procedure found that the risk of miscarriage in the study group was increased by 1.0% (95% CI, 0.3–1.5%)[1]. CVS has been compared to amniocentesis, and several studies have concluded that the miscarriage risk following the two procedures is comparable[2–5].

The size of the needles used for the invasive procedures has remained unchanged over the last 20 years, but ultrasound machines have been developed to give a much higher image resolution, and the number of procedures performed has increased. Many clinicians today therefore do not believe that the miscarriage rate related to these invasive procedures is as high as 1%, and a large number of mostly uncontrolled studies[6,7] have found a lower procedure-related risk, a recent article even suggesting that the risk associated with amniocentesis is as low as 1 in 1600[8].

The aim of our study was to investigate the miscarriage rate after amniocentesis or transabdominal CVS in an unselected group of women. It is practically and ethically impossible to conduct a randomized trial with the sample size required to detect a risk reduction from 1.0% to 0.5%. We therefore performed a nationwide registry study over 11 years including all singleton pregnancies in Denmark in which an invasive test had been performed.

PATIENTS AND METHODS

In Denmark all citizens have a unique personal identification number (PIN) in the civil registration system, which enables linkage between different registries.

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Accepted: 14 February 2009

When an amniocentesis or CVS is performed, the laboratory performing the chromosome analysis reports its result to the Danish Central Cytogenetic Registry (DCCR). In Denmark the outcome of any pregnancy (discharge diagnosis) has to be reported to the National Registry of Patients (NRP), using the World Health Organization's International Classification of Diseases (ICD) (since 1994 ICD-10). All deliveries, miscarriages and terminations of pregnancy (TOP) at public or private hospitals are recorded in the NRP.

The study included all singleton pregnancies in Denmark in which an amniocentesis or CVS had been performed between January 1, 1996 and December 31, 2006. The indications for prenatal diagnosis were primarily maternal age ≥ 35 years, prior pregnancy with chromosome abnormality, or hereditary disease in the family. In 2004 the National Board of Health issued new guidelines regarding prenatal screening and diagnosis, recommending that all women be offered a risk assessment for Down syndrome by combined first-trimester screening, and only an invasive procedure if the risk of Down syndrome was above a defined cut-off. This policy was implemented between 2004 and 2006 using a cut-off of 1 : 300 at the time of testing.

All invasive procedures were performed under ultrasound guidance, and CVS was only done transabdominally. During this 11-year study period 697 515 births were registered in the whole country. The study included all 64 207 singleton pregnancies between 1996 and 2006 in which an amniocentesis or a CVS had been performed and for which information about gestational age at the time of the procedure was available. Four hundred and forty-four (0.7%) women had been excluded owing to missing information about gestational age at the time of amniocentesis or CVS. The PIN codes of all women having an invasive procedure, as well as the procedure date, hospital and gestational age, were retrieved from the NRP and linked by PIN to data from the DCCR.

In the NRP an outcome of every pregnancy was sought from the day after the invasive procedure. The outcome was classified as miscarriage if it happened before 24 weeks' gestation (ICD codes DO03 and DO021), TOP (before 12 weeks (DO04) or after 12 weeks (DO05)), delivery of a liveborn child (DO60-83), intrauterine death from 24 weeks until delivery (P95) or stillbirth (DZ371), if recorded within 26 weeks after amniocentesis or within 30 weeks after CVS. The postprocedural miscarriage rate was defined as spontaneous abortion or intrauterine demise before 24 weeks of gestation. Total pregnancy loss was defined as spontaneous abortion, intrauterine death or stillbirth. The study was approved by the Danish Data Protection Agency, but approval from the ethics committee was not required, as this was a registry study.

Assessment of miscarriage rate in pregnancies without an invasive test

We attempted to assess the miscarriage rate in the 633 308 women not undergoing an invasive procedure, in order to have a background rate with which to compare the miscarriage rate following an invasive test. It was however not possible to define a common starting point from which all pregnancies, without selection, could be included with an ultrasonically verified live pregnancy. Between weeks 11 and 24 there were 25 063 miscarriages among the 633 308 women who could have undergone CVS, corresponding to a miscarriage rate of 4.0%. Among the women who were still pregnant at 15 weeks and could have had an amniocentesis there were 5692 miscarriages, corresponding to a rate of 0.9%.

Statistical analysis

We used χ^2 tests to compare distributions between groups, and considered a probability of $P < 0.05$ as statistically significant. An unadjusted logistic regression model was specified to evaluate whether the number of invasive procedures a department performs affects the risk of miscarriage. Departments were classified according to the number of procedures performed in the 11-year study period: < 500 CVS or amniocenteses, 501–1000, 1001–1500, and > 1500. Odds ratios (OR) are reported, i.e. the estimated differences in risk between the four categories, with the reference being departments with more than 1500 procedures, for which the OR was set as 1.

RESULTS

From 1996 to 2006 a total of 32 852 amniocenteses and 31 355 CVS were performed (Figure 1). The yearly number of invasive procedures declined during the study period from 6924 (10.8% of the total) to 3102 (4.8% of the total) ($P < 0.0001$). The proportion of amniocenteses decreased from 55% to 31% throughout the period, while that of CVS increased from 45% to 69% ($P < 0.0001$). A total of 19 departments performed amniocentesis/CVS during the study period. One department (Rigshospitalet) performed 22 455 procedures, corresponding to 35% of all procedures, while the number varied between 465 and 4102 at the other 18 departments.

The distribution of gestational age at the time of the procedure is shown in Table 1. There was a decline in the proportion of amniocenteses being performed before 15 weeks' gestation ($P < 0.0001$), and an increase in the proportion of amniocenteses performed after 18 weeks through the study period ($P < 0.0001$). As regards CVS, there was a significant shift towards a later gestational age, and from 2005 87% of the procedures were performed in week 11 or later. The indications for amniocentesis and CVS were maternal age ≥ 35 years (57.7%); previous child with chromosome abnormality (3.4%); parent carrier of chromosome abnormality (1.1%); chromosome abnormality in the family (5.0%); mental retardation in a previous child or in the family (2.0%); increased risk of monogenic disease (3.3%); increased risk of open fetal malformation i.e. neural tube defect or abdominal wall defect (2.1%); increased risk of chromosomal abnormality following a triple test (6.1%), an ultrasound

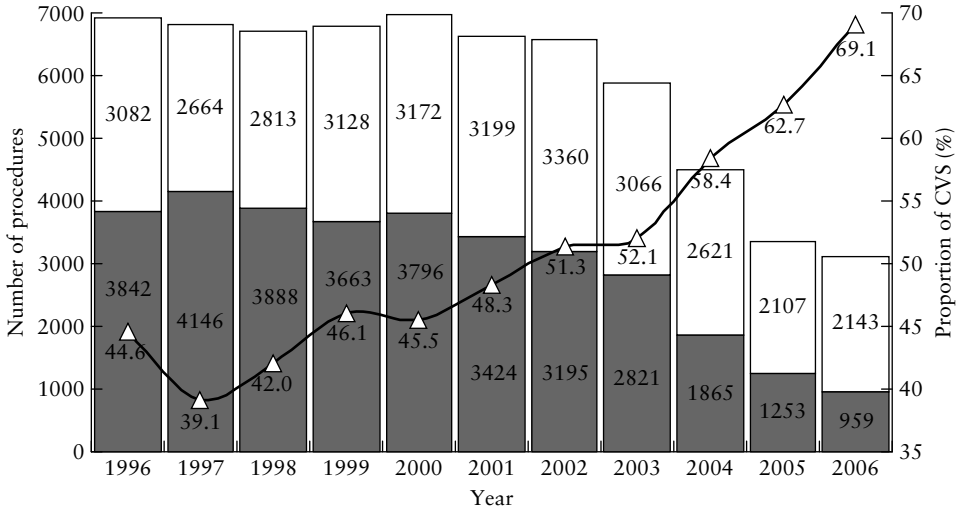

Figure 1 Number of amniocenteses (■) and chorionic villus samplings (CVS; □) performed in singleton pregnancies yearly from 1996 to 2006 in Denmark, and the proportion of CVS as a percentage of all invasive tests (△).

Table 1 Distribution of gestational age at the time of amniocentesis and transabdominal chorionic villus sampling in Denmark in the period 1996–2006

Time period	*Amniocentesis*					*Chorionic villus sampling*			
	< 15 weeks	*15–16 weeks*	*17–18 weeks*	*> 18 weeks*	*Total*	*< 9 weeks*	*9–10 weeks*	*≥ 11 weeks*	*Total*
1996–1998	3277 (27.6)	6110 (51.4)	1846 (15.5)	643 (5.4)	11 876	43 (0.5)	4355 (50.9)	4161 (48.6)	8559
1999–2001	2890 (26.6)	5739 (52.7)	1586 (14.6)	668 (6.1)	10 883	32 (0.3)	4107 (43.3)	5360 (56.4)	9499
2002–2004	799 (10.1)	5248 (66.6)	1201 (15.2)	633 (8.0)	7881	87 (1.0)	3293 (36.4)	5667 (62.6)	9047
2005–2006	141 (6.4)	1385 (62.6)	322 (14.6)	364 (16.5)	2212	33 (0.8)	519 (12.2)	3698 (87.0)	4250
Overall	7107 (21.6)	18 482 (56.3)	4955 (15.1)	2308 (7.0)	32 852	195 (0.6)	12 274 (39.1)	18 886 (60.2)	31 355

Data are given as *n* (% of the total for the time period).

Table 2 Maternal age at the time of amniocentesis and chorionic villus sampling in Denmark in the period 1996–2006

Time period	*Amniocentesis*				*Chorionic villus sampling*			
	< 30 years	*30–34 years*	*≥ 35 years*	*Total*	*< 30 years*	*30–34 years*	*≥ 35 years*	*Total*
1996–1998	2056 (17.3)	3116 (26.2)	6704 (56.4)	11 876	859 (10.0)	1446 (16.9)	6254 (73.1)	8559
1999–2001	1355 (12.5)	2840 (26.1)	6688 (61.5)	10 883	729 (7.7)	1306 (13.7)	7464 (78.6)	9499
2002–2004	925 (11.7)	1734 (22.0)	5222 (66.3)	7881	716 (7.9)	1253 (13.8)	7078 (78.2)	9047
2005–2006	435 (19.7)	592 (26.8)	1185 (53.6)	2212	824 (19.4)	1239 (29.2)	2187 (51.5)	4250
Overall	4771 (14.5)	8282 (25.2)	19 799 (60.3)	32 852	3128 (10.0)	5244 (16.7)	22 983 (73.3)	31 355

Data are given as *n* (% of the total for the time period).

scan (3.0%) or a combined first-trimester risk assessment (3.8%); malformation on ultrasound (3.9%); and miscellaneous (8.5%).

Table 2 shows the maternal age at the time of amniocentesis and CVS. Overall 66.6% of the procedures were performed in women aged 35 years or more, but the proportion of invasive tests performed in this age group decreased at the end of the study period ($P < 0.0001$). If the study population is divided into 5-year age groups, the proportions of amniocentesis and CVS performed in women aged 16–20 years were 0.6% and 0.3%, in women aged 21–25 years 4.2% and 2.6%, in women aged 26–30 years 13.3% and 9.6%, in women aged 31–35 years 35.9% and 29.2%, in women aged 36–40 years 41.0% and 51.0%, in women aged 41–45 years 4.9% and 7.1%, and in women aged 46–50 years 0.1% and 0.1%.

Table 3 shows the outcome of pregnancy after an invasive test in the four different time periods. The postprocedural miscarriage rate following amniocentesis decreased slightly from 1.5% to 1.2% ($P = 0.25$) through the study period, while that of CVS decreased from 2.4% to 1.9% ($P = 0.06$) (Figure 2). Overall, 457 miscarriages (1.4%; 95% CI, 1.3–1.5) occurred following

Table 3 Outcome of pregnancy following amniocentesis (AC) or chorionic villus sampling (CVS) in different time periods between 1996 and 2006 in Denmark

	1996–1998		*1999–2001*		*2002–2004*		*2005–2006*	
Parameter	*AC*	*CVS*	*AC*	*CVS*	*AC*	*CVS*	*AC*	*CVS*
Miscarriage	177 (1.5)	205 (2.4)	160 (1.5)	150 (1.6)	94 (1.2)	154 (1.7)	26 (1.2)	80 (1.9)
Intrauterine death	74 (0.6)	34 (0.4)	53 (0.5)	34 (0.4)	46 (0.6)	44 (0.5)	21 (0.9)	17 (0.4)
Termination	292 (2.5)	332 (3.9)	274 (2.5)	360 (3.8)	237 (3.0)	458 (5.1)	127 (5.7)	428 (10.1)
Live birth	11 333 (95.4)	7988 (93.3)	10 396 (95.5)	8955 (94.3)	7504 (95.2)	8391 (92.7)	2038 (92.1)	3725 (87.6)
Total	11 876	8559	10 883	9499	7881	9047	2212	4250

Data are given as *n* (% of the total for the time period).

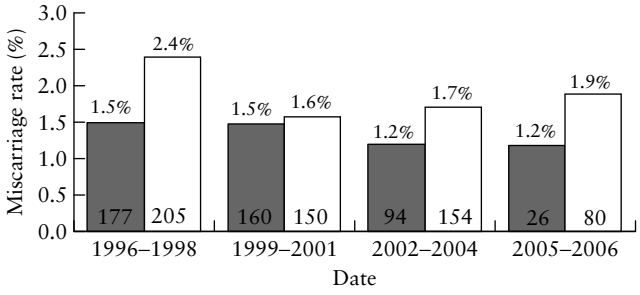

Figure 2 Postprocedural miscarriage rate following amniocentesis (■) and chorionic villus sampling (□) between 1996 and 2006 in Denmark.

amniocentesis, while 589 (1.9%; 95% CI, 1.7–2.0) occurred following CVS. If pregnancies with the outcome of TOP are excluded, the miscarriage rate following amniocentesis remained at 1.4% (95% CI, 1.3–1.6), while it increased to 2.0% following CVS (95% CI, 1.8–2.1). A total of 651 pregnancies (corresponding to a total loss rate of 2.0%; 95% CI, 1.8–2.1%) ended with a miscarriage or intrauterine death following amniocentesis and 718 following CVS (2.3%; 95% CI, 2.1–2.5%).

The proportion of TOPs following an invasive diagnostic procedure increased throughout the study period, from 2.5% to 5.7% following amniocentesis ($P < 0.0001$), and from 3.9% to 10.1% following CVS ($P < 0.0001$) (Table 3). Overall the rate of TOP following an invasive procedure was 3.1%, 3.1%, 4.1% and 8.6% in the four time periods, respectively.

There was no significant correlation between maternal age and postprocedural fetal loss rate, neither overall, nor after stratification into amniocentesis and CVS ($P = 0.07$) (Table 4).

The correlation between the postprocedural miscarriage rate and the number of amniocenteses and CVS performed in the different departments of obstetrics and gynecology in Denmark is shown in Figure 3. The estimated ORs were calculated after excluding the largest department (Rigshospitalet). Similar results were obtained when the largest department was included. The number of procedures a department performed had a significant effect on the risk of fetal loss, for CVS as well as for amniocentesis. For amniocentesis the OR for risk of miscarriage was significantly elevated if the department

Table 4 Postprocedural miscarriage rate per 100 pregnancies following amniocentesis (AC) and transabdominal chorionic villus sampling (CVS) in four time periods, according to maternal age

	Maternal age (years)					
	< 30		*30–34*		*> 34*	
Time period	*AC*	*CVS*	*AC*	*CVS*	*AC*	*CVS*
1996–1998	1.1	1.2	1.4	2.2	1.7	2.6
1999–2001	1.3	1.4	1.4	1.5	1.6	1.6
2002–2004	2.2	1.3	1.3	1.0	1.0	1.9
2005–2006	2.3	2.3	0.8	2.0	0.9	1.6
Overall	1.5	1.5	1.3	1.7	1.4	2.0

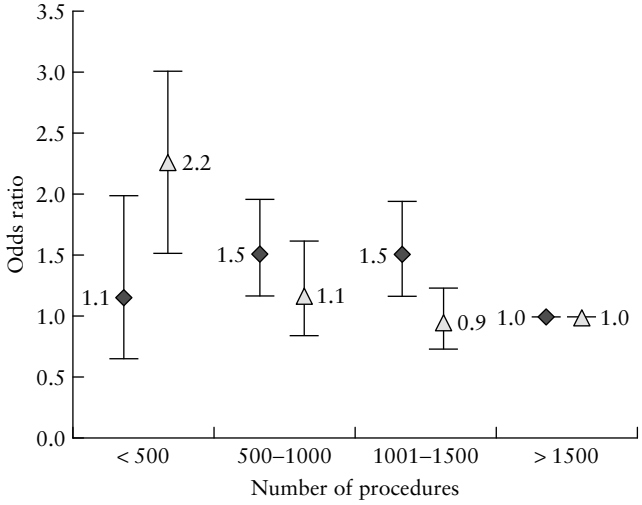

Figure 3 Postprocedural risk of fetal loss (odds ratio (OR) with 95% CI) after chorionic villus sampling (◆) and amniocentesis (△) according to number of procedures performed in the 11-year study period. Departments performing > 1500 procedures were used as a reference group, and their OR set at 1.

performed fewer than 500 procedures compared to more than 1500 procedures. The OR for the two remaining groups was not significantly different from 1. As regards CVS, the risk of fetal loss was significantly greater in departments performing 500–1000 and 1001–1500 when compared with those performing more than 1500 procedures over the 11 years. If departments performing 0–1000 CVS are compared with departments performing

more than 1500 procedures, the risk of miscarriage was also significantly greater (OR 1.4; 95% CI, 1.1–1.8).

DISCUSSION

In this cohort study of more than 60 000 singleton pregnancies having amniocentesis or CVS, the postprocedural fetal loss rates before 24 completed weeks' gestation were 1.4% and 1.9%, respectively, and total fetal loss rates were 2.0% and 2.3%, respectively. The differences between loss rates following amniocentesis and CVS may be explained by the difference in gestational age at the time of the procedures[9]. The fetal loss rate figures consist of a procedure-related loss rate plus the spontaneous miscarriage rate. The procedure-related fetal loss after amniocentesis performed at a mean gestational age of 16 weeks was estimated to be 1.0% in a randomized trial comparing amniocentesis in the study group with ultrasonography in the control group[1]. Some case–control studies of women at increased risk for Down syndrome have failed to show an increased risk of miscarriage associated with second-trimester amniocentesis, but those studies often lacked sufficient power to identify small differences[6,7,10,11]. On the other hand, early amniocentesis, defined as amniocentesis performed at between 9 and 14 weeks, was shown in two randomized trials to carry a significantly higher risk of fetal loss than either CVS or amniocentesis performed in week 16 or later[12,13]. Although the proportion of amniocenteses performed before 15 weeks in the present study decreased throughout the study period, it still constituted 21.6% overall. The very low risk of 1 in 1600 attributable to amniocentesis suggested by the FASTER trial[8] may be due to the use of a nonrandomized control group, a source of considerable bias[14].

The fetal loss rate following CVS has not been compared in randomized trials with no invasive testing, but was found to be comparable to the fetal loss rate after amniocentesis[3–5]. A Cochrane review of amniocentesis and CVS thus concluded that the total pregnancy loss after transabdominal CVS is comparable to that after second-trimester amniocentesis, but that early amniocentesis has a higher rate of pregnancy loss[15].

The most recent systematic review of the procedure-related complications of amniocentesis and CVS included 29 observational studies published after 1995 on amniocentesis and 16 studies on CVS. Pregnancy loss before 24 weeks was 0.9% following amniocentesis and 1.3% following CVS, but with wide variation between studies[14]. Mujezinovic and Alfirevic[14] found that total pregnancy loss was 1.9% and 2.0% following amniocentesis and CVS, respectively, quite similar to the figures from the present study. The spontaneous fetal loss rate is difficult to estimate for the general population, as recruitment to studies may have been biased, and differences in methods used to confirm a pregnancy's viability, time interval between an ultrasound scan showing a live fetus and fetal demise, definition of fetal loss and length of follow-up may also contribute to the variation[16]. Indeed we could not include a control group of women with live fetuses on ultrasound scan at the same gestational age, because women who had a missed miscarriage diagnosed at the time of amniocentesis or CVS and who therefore did not have an invasive procedure performed, could not be excluded. When the new guidelines for prenatal screening and diagnosis are fully implemented in Denmark[17], a background rate of miscarriage after identification of a live fetus in weeks 11–13 may be assessed, although this estimated risk will also be skewed as those pregnancies with a risk for Down syndrome above the cut-off at which women are offered an invasive test will for the most part have an invasive test. Those pregnancies at highest risk of spontaneous miscarriage will thus be excluded, but a minimum spontaneous fetal loss rate may be assessed following a normal ultrasound scan at around 12 weeks.

In the aforementioned randomized trial of amniocentesis, the control group had a 0.7% rate of fetal loss from week 16[1], and the same rate was found in a French study of 3472 women having amniocentesis compared to 47 004 controls[18]. Termination of chromosomally abnormal pregnancies in the first and early second trimesters also influences the fetal loss rate later in pregnancy, as these fetuses would have had a significantly increased risk of intrauterine demise[9]. It may be concluded that although the present study cannot give a precise estimate of the procedure-related risk of amniocentesis and CVS, our data are in accordance with those from previously performed randomized trials, i.e. between 0.5% and 1.0%. Furthermore there does not seem to be any major difference in fetal loss rate between the two procedures.

In contrast to other studies[9,12,19], we did not find any association between maternal age and miscarriage rate. This could be explained by our assessment of fetal viability at the time of the invasive procedure (either week 11 or week 15) instead of earlier in pregnancy[12] or not having fetal viability evaluated before entry to the study[9]. Our data suggest that the increased risk of miscarriage in older women occurs before the time of amniocentesis, while there may still be a trend towards an increased miscarriage risk at the time of CVS in older women.

The introduction of first-trimester risk assessment in Denmark during the period 2004–2006 has resulted in a shift towards CVS as a diagnostic test[17]. Restricting invasive tests to women at an increased risk has more than halved the proportion of women having an invasive test from 10.6% to 4.9%. The odds of having a fetus with a chromosomal abnormality, measured as the proportion of women having a TOP following the invasive test, increased even more markedly. In the period 1996–2001 3.9% of women had a TOP following CVS, while the figure was 10.1% in the period 2005–2006. The odds of having a TOP following amniocentesis were also more than doubled during the study period, probably because more pregnancies are referred for amniocentesis following an abnormal 18–20-week scan.

The decreasing number of procedures overall has been used as an argument for centralization, as

experience may decrease the procedure-related fetal loss[20]. Thus, Wijnberger *et al.* found that the frequency of unintended fetal loss following CVS decreased with increasing experience[20], while Leschot *et al.* found a higher miscarriage rate following amniocentesis when the procedure was performed by less experienced operators[21]. In the present study the fetal loss rate was higher in departments performing fewer than 1500 procedures over the 11-year study period compared with those performing more than 1500. Although the study does span a long period of time, both techniques had been well developed by the start of the study period. However obstetricians in different centers may still be on their learning curve. 1500 procedures over 11 years corresponds to fewer than three procedures per week, and could be considered an absolute minimum (to keep the miscarriage rate as low as possible), especially as there is usually more than one operator in each center. With the current number of invasive prenatal diagnostic procedures in Denmark, each center would perform around 150 procedures per year if they were evenly distributed. This may not be a sufficient number to maintain expertise as well as educate new operators, and speaks in favor of centralizing these procedures.

We acknowledge that our study had some limitations. It was based on reports to the NRP from all departments of obstetrics and gynecology in the country. The outcomes 'intrauterine death' and 'live birth' are unlikely to be misclassified. It is, however, impossible to rule out misclassification between miscarriage and TOP. This could occur in pregnancies affected by complications following an invasive procedure, such as severe bleeding or anhydramnios due to leakage. These pregnancies could be terminated and classified as such instead of as miscarriages. This would, however, only underestimate our estimated procedure-related fetal loss rate.

The strengths of the study were the nationwide design and the compulsory Danish cytogenetic registry and NRP. These two registries allowed us to identify all pregnancies in which a CVS or an amniocentesis had been performed in the study period and to follow them to a clinical outcome.

In conclusion, this is the largest national report to date assessing pregnancy loss following amniocentesis and CVS. It shows that the postprocedural fetal loss rate was 1.4% after amniocentesis and 1.9% after CVS, and that the number of procedures performed per center has an impact on the fetal loss rate.

REFERENCES

1. Tabor A, Madsen M, Obel E, Philip J, Bang J, Nørgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; **1**: 1287–1293.
2. Smidt-Jensen S, Permin M, Philip J, Lundsteen C, Zachary JM, Fowler SE, Grüning K. Randomised comparison of amniocentesis and transabdominal and transcervical chorionic villus sampling. *Lancet* 1992; **340**: 1237–1244.
3. Canadian Collaborative CVS-Amniocentesis Clinical Trial Group. Multicentre randomised clinical trial of chorionic villus sampling and amniocentesis. First report. *Lancet* 1989; **1**: 1–6.
4. Rhoads GG, Jackson LG, Schesselman SA, de la Cruz FF, Desnick RJ, Golbus MS, Ledbetter DH, Lubs HA, Mahoney MJ, Pergament E. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. *N Engl J Med* 1989; **320**: 610–617.
5. MRC Working Party on the Evaluation of Chorion Villus Sampling. Medical Research Council European Trial of chorion villus sampling. *Lancet* 1991; **337**: 1491–1499.
6. Caughey AB, Hopkins LM, Norton ME. Chorionic villus sampling compared with amniocentesis and the difference in the rate of pregnancy loss. *Obstet Gynecol* 2006; **108**: 612–616.
7. Odibo AO, Gray DL, Dicke JM, Stamilio DM, Macones GA, Crane JP. Revisiting the fetal loss rate after second-trimester genetic amniocentesis. *Obstet Gynecol* 2008; **111**: 589–595.
8. Eddleman KA, Malone FD, Sullivan L, Dukes K, Berkowitz RL, Kharbutli Y, Porter TF, Luthy DA, Comstock CH, Saade GR, Klugman S, Dugoff L, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, D'Alton ME. Pregnancy loss rates after midtrimester amniocentesis. *Obstet Gynecol* 2006; **108**: 1067–1072.
9. Snijders RJ, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age- and gestation-specific risk for trisomy 21. *Ultrasound Obstet Gynecol* 1999; **13**: 167–170.
10. Tongsong T, Wanapirak C, Sirivatanapa P, Piyamongkol W, Sirichotiyakul S, Yampochai A. Amniocentesis-related fetal loss: A cohort study. *Obstet Gynecol* 1998; **92**: 64–67.
11. Seeds JW. Diagnostic mid trimester amniocentesis: How safe? *Am J Obstet Gynecol* 2004; **191**: 608–616.
12. Nicolaides K, Brizot Mde L, Patel F, Snijders R. Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks' gestation. *Lancet* 1994; **344**: 435–439.
13. Canadian Early and Mid-trimester Amniocentesis Trial (CEMAT) Group. Randomised trial to assess safety and fetal outcome of early and midtrimester amniocentesis. *Lancet* 1998; **351**: 242–247.
14. Mujezinovic F, Alfirevic Z. Procedure-related complications of amniocentesis and chorionic villus sampling. A systematic review. *Obstet Gynecol* 2007; **110**: 687–694.
15. Alfirevic Z, Sundberg K, Brigham S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. *The Cochrane Database of Systematic Reviews* 2003; Issue (1):. Art. No.: CD003252. DOI: 10.1002/14651858.CD003252.
16. Hoesli IM, Walter-Goebel I, Tercanli S, Holzgreve W. Spontaneous fetal loss rates in a non-selected population. *Am J Med Genet* 2001; **100**: 106–109.
17. Ekelund CK, Jørgensen FS, Petersen OB, Sundberg K, Tabor A; Danish Fetal Medicine Research Group. Impact of a new national screening policy for Down's syndrome in Denmark: a population based cohort study. *BMJ* 2008; **337**: a2547.
18. Muller F, Thibaud D, Poloce F, Gelineau MC, Bernard M, Brochet C, Millet C, Réal JY, Dommergues M. Risk of amniocentesis in women screened positive for Down syndrome with second trimester maternal serum markers. *Prenat Diagn* 2002; **22**: 1036–1039.
19. Nybo Andersen AM, Wohlfahrt M, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000; **320**: 1708–1712.
20. Wijnberger LDE, van der Schouw YT, Christiaens GCML. Learning in medicine: chorionic villus sampling. *Prenat Diagn* 2000; **20**: 241–246.
21. Leschot NJ, Verjaal M, Treffers PE. Risks of midtrimester amniocentesis: assessment in 3,000 pregnancies. *Br J Obstet Gynaecol* 1985; **92**: 804–807.