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PREGNANCY LOSS AFTER AMNIOCENTESIS AND CHORIONIC VILLUS SAMPLING: COHORT STUDY

NEUSPELA NOSEČNOST PO AMNIOCENTEZI IN BIOPSIJI HORIONSKIH RESIC: KOHORTNA ŠTUDIJA

Ivana PALJK LIKAR[1,2], Ksenija SLAVEC JERE[1], Teja MOŽINA[1], Ivan VERDENIK[1], Nataša TUL[3*]

[1]University Medical Centre Ljubljana, Department of Perinatology, Division of Obstetrics and Gynecology, Šlajmerjeva ulica 3, 1000 Ljubljana, Slovenia
[2]University of Ljubljana, Faculty of Medicine, Vrazov trg 2, 1000 Ljubljana, Slovenia
[3]Women's Hospital Postojna, Prečna ulica 4, 6230 Postojna, Slovenia

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ABSTRACT

Introduction: Introduction: To estimate the procedure-related risks of pregnancy loss following chorionic villus sampling (CVS) and amniocentesis (AC) compared to pregnancies without procedure.

Methods: This cohort study enrolled all women who underwent CVS or AC at the Department of Perinatology, University Medical Centre, Ljubljana, Slovenia (from January 2013 to June 2015). For each group we obtained a maternal age and gestational age (11–14 weeks for CVS and >15 weeks for AC) for a matched control group without invasive procedures from the national database. The data was obtained from hospital records and telephone surveys concerning pregnancy outcomes. Pregnancy loss rates in intervention vs. control groups were compared by generating relative risk (RR) with a 95% confidence interval.

Results: During the study period, 828 women underwent CVS and 2,164 women underwent AC. Complete outcome data was available in 2,798 cases (93.5%, 770 CVS, 2,028 AC). Pregnancy loss occurred in 8/770 (1.04%, 95% CI 0.4–2.0%) after CVS vs. 15/1130 (1.33%, 95% CI 0.8–2.2%) in matched control (RR 0.8, 95% CI 0.33–1.8, p=0.6). It occurred in 16/2028 (0.79%, 95% CI 0.5–1.3%) after AC vs. 14/395 (3.29%, 95% CI 2.1–5.8%) in matched control (RR 0.2, 95% CI 0.11–0.45, p<0.0001).

Conclusion: The pregnancy loss rates after CVS and AC were comparable to losses in pregnancies without these procedures. With the increasing use of non-invasive prenatal testing, information that the invasive procedures are safe when indicated is essential.

Keywords: pregnancy loss, amniocentesis, chorionic villus sampling, prenatal diagnosis

IZVLEČEK

Uvod: *Namen raziskave je bil oceniti tveganje za zaplete po biopsiji horionskih resic (CVS) in amniocentezi (AC) ter ga primerjati z zapleti v nosečnostih brez tega posega.*

Metode: *V kohortno študijo smo vključili vse nosečnice, ki so imele CVS ali AC na Kliničnem oddelku za perinatologijo univerzitetnega kliničnega centra v Ljubljani med januarjem 2013 in junijem 2015. Skupini nosečnic po CVS in AC smo primerjali s skupinami nosečnic iz nacionalne podatkovne baze nosečnic brez invazivnega posega in je bila primerljiva v maternalni in gestacijski starosti (11-14 tednov za CVS in > 15 tednov za AC). Podatke za skupini po CVS in AC smo pridobili iz bolnišnične dokumentacije in preko telefonskega pogovora o izidu nosečnosti. Pogostost neuspele nosečnosti smo primerjali s kontrolno skupino z uporabo relativnega tveganja (RR) in s 95-odstotnim konfidenčnim intervalom.*

Rezultati: *Vključili smo 828 nosečnic po CVS in 2.164 nosečnic po AC. Vključili smo 2798 (93,5 %, 770 po CVS, 2028 po AC) primerov, za katere smo pridobili popolne podatke o izidu nosečnosti. Do zapletov je prišlo v 8 od 770 primerov po CVS (1,04 %, 95 % CI 0,4-2,0 %) in v 15 od 1130 primerov (1,33 %, 95 % CI 0,8-2,2 %) v primerljivi skupini brez invazivnega posega (RR 0,8, 95 %, CI 0,33-1,8, p = 0,6). Do zapletov je prišlo v 16 od 2.028 primerih po AC (0,79 %, 95 % CI 0,5-1,3 %) in v 14 od 395 primerih v primerjavi s primerljivo skupino brez invazivnega posega, (3,29 %, 95 % CI 2,1-5,8 %) (RR 0,2, 95 % CI 0,11-0,45, p < 0,0001).*

Zaključek: *Pogostost zapletov po CVS in AC je bila primerljiva s številom zapletov v nosečnostih brez invazivnega posega. Z naraščanjem uporabe neinvazivnih predrojstnih testov je informacija pri svetovanju pacientkam pred invazivnimi posegi, da so ti varni ob ustrezni indikaciji, ključna.*

Ključne besede: *zapleti, neuspela nosečnost, amniocenteza, biopsija horionskih resic, prenatalna diagnostika*

***Corresponding author:** Tel. + 386 40 257 928; E-mail: natasa.tul@guest.arnes.si

1 INTRODUCTION

Chorionic villus sampling (CVS) and amniocentesis (AC) are the most commonly performed invasive procedures in foetal medicine (1–3). The most important factor influencing the uptake of invasive procedures is procedure-related pregnancy loss (4). In recent years, the procedure-related pregnancy loss rate has been reported to vary in CVS and AC between 0.2% and 1% (1–5). However, informed consent requires accurate comparative information capable of guiding pregnant women concerning relative procedure-related pregnancy vs. pregnancies without procedures.

Papers evaluating this topic have been collated in a recent systematic review (1). The limitations stated by the reviewers included "biases introduced owing to differences in study design, inclusion of studies carried out over a period of time, publication bias, heterogeneity between studies and methods used for the analysis of data". Furthermore, the reviewers specified that they were unable to derive estimates of procedure-related loss due to the "inability to adjust for maternal and pregnancy characteristics in the invasive and control groups". This limits the ability to generalise findings for use of this data for the purpose of counselling mothers.

Our work was therefore aimed at overcoming this deficiency in order to generate unbiased estimates of procedure-related pregnancy loss risk following CVS and AC compared to matched control pregnancies without the procedures.

2 METHODS

2.1 Data sources

AC has been performed at the Department of Perinatology at Ljubljana University Medical Centre since 1981. This cohort study included all women who underwent CVS or AC at the department between January 2013 and June 2015. Data on maternal age, indications for the procedure, obstetric history, gestational age at the time of procedure and pregnancy outcome was obtained from the hospital database. In cases where the outcome was not recorded, it was obtained by a short personal telephone interview. The background risk of miscarriage was obtained from the National Institute of Public Health, which collects data according to reported diagnoses sorted in accordance with the International Classification of Diseases. All women in Slovenia who experienced spontaneous miscarriage at the same time of gestation (weeks 11–14 of gestation for CVS and after week 15 of gestation for AC) between January 2013 and 2015 were included.

2.2 Definitions

Procedure-related complications were divided into four categories: pregnancy loss, chorioamnionitis with delivery after the 37th week of gestation, pre-term premature rupture of membranes (PPROM) and other (minor) complications without clinical significance (cramping, vaginal spotting, pain after the procedure, minimal amniotic fluid leakage).

Pregnancy loss as a procedure-related complication was defined as any foetal loss or known chorioamnionitis with subsequent foetal demise in the four weeks following the procedure.

Pregnancy outcome was categorised as: pregnancy loss, induced termination of pregnancy, delivery <37th week of gestation and delivery ≥37th week of gestation.

The primary endpoint of our study was the procedure-related pregnancy loss rate. We defined it as the total pregnancy loss rate in the four weeks following the procedure, minus the background risk in a group of women who did not undergo any of the procedures. The background risk was obtained from the National Institute of Public Health.

2.3 Data analysis

The acquired data was entered in a Microsoft® Office Excel spreadsheet and statistically analysed using IBM SPSS Statistics for Windows.

Pearson's chi-squared test was used to compare the pregnancy loss rate in the two groups. A p-value of less than 0.05 was defined as statistically important.

All the participants signed an informed consent form before the procedure. The study was approved by Slovenian National Medical Ethics Committee.

3 RESULTS

A total of 2,992 procedures were performed. Pregnancy outcome was available for analysis in 2,798 cases (93.5%). In 194 cases (6.5%), pregnancy outcome was not recorded in the database: 17 (0.6%) declined to participate in the telephone survey and the remaining 177 (5.9%) were unreachable (wrong/old phone number, unanswered calls, moved abroad).

The characteristics of the women included and their complications after CVS and AC are presented in Table 1. The pregnant women were between 19 and 48 years old, with a mean age of 35.4 years.

3.1 Complications after AC or CVS

In the group of 770 women who had CVS, pregnancy loss occurred in eight cases (1.04%, 95% CI 0.4–2.0%). There were 29 cases (3.8%, 95% CI 2.6–5.3%) of minor complications. There was one case of chorioamnionitis with delivery after the 37th week of gestation, while 732 women (95.1%) did not experience any complications.

Table 1. Characteristics and subsequent complications in the CVS and AC group given as a number and percentage.

Variables		CVS	AC
Baseline characteristics	**Gravida**		
	Primipara	207 (25.0%)	536 (24.8%)
	Multipara	621 (75.0%)	1,628 (75.2%)
	Previous miscarriage		
	None	468 (56.5%)	1,214 (56.1%)
	≤2	327 (39.5%)	841 (38.9%)
	>2	33 (4.0%)	109 (5.0%)
	Indications		
	Advanced maternal age	290 (35.0%)	1,308 (60.4%)
	Positive result at screening test	363 (43.8%)	367 (17.0%)
	Ultrasound abnormality	12 (1.4%)	163 (7.5%)
	Genetic syndrome in family	84 (10.1%)	78 (3.6%)
	More than one indication	76 (9.2%)	164 (7.6%)
	Toxoplasma gondii seroconversion	0 (0.0%)	56 (2.6%)
	On demand	2 (0.2%)	19 (0.9%)
	Other	1 (0.1%)	9 (0.4%)
Complications	No complications	732 (95.1%)	1,924 (94.9%)
	Minor complications	29 (3.8%)	75 (3.7%)
	Chorioamnionitis with delivery at term	1 (0.1%)	1 (0.0%)
	PPROM	0 (0.0%)	12 (0.6%)
	Miscarriage after procedure	8 (1.04%)	16 (0.8%)

In the group of 2,028 women who underwent AC, pregnancy loss was noticed in 16 cases (0.8%, 95% CI 0.5–1.3%), 12 women (0.6%, 95% CI 0.3–1.0%) experienced PPROM, and in 75 cases (3.7%, 95% CI 2.9–4.6%) there were minor complications. There was one case of chorioamnionitis delivery after the 37th week of gestation. The majority of women who underwent AC (94.9%) experienced no complications (Table 1). The result of foetal karyotyping after AC or CVS was normal in 2,598 cases (86.7%). In 154 cases (5.5%), termination of pregnancy was requested.

3.2 Risk of pregnancy loss

CVS was performed between the 11th and 14th weeks of gestation. Between 2013 and 2015, there were 1,130 spontaneous miscarriages (1.8% of all pregnancies) in the same period of gestation. Pregnancy loss among women after CVS occurred in 8/770 (1.04%, 95% CI 0.4–2.0%) compared to 15/1130 (1.33%, 95% CI 0.8–2.2%) in the matched control group (RR 0.8, 95% CI 0.33–1.8, p=0.6). There was no statistically significant difference between the CVS-related risk of miscarriage and the background risk of spontaneous miscarriage (chi-squared test, p=0.076).

AC was performed after the 16th week of gestation. Between 2013 and 2015, 395 spontaneous miscarriages were reported after the 15th week of gestation (0.78% of all pregnancies). Pregnancy loss occurred in 16/2028 AC procedures (0.79%, 95% CI 0.5–1.3%) compared to 14/395 (3.29%, 95% CI 2.1–5.8%) in the matched control group (RR 0.2, 95% CI 0.11–0.45, p<0.0001). There was no statistically significant difference between the AC-related risk of miscarriage and the background risk of spontaneous miscarriage (chi-squared test, p=0.344).

4 DISCUSSION

At our centre, pregnancy loss after CVS and AC was found to be lower than had commonly been reported in the past, and is comparable to the results reported in recent studies (1, 2, 4–6). It is interesting to note that, at our centre, fewer miscarriages occurred four weeks after CVS and AC procedures than would have been expected, with the percentage being comparable to the background risk. This information is essential for patient counselling, as the rates currently communicated to women are higher, which can discourage them from undergoing the procedure.

Mental health in the peripartum period is hugely important for women and their developing offspring, as stress anxiety, and depression during pregnancy are associated with alterations in foetal and infant neurobehavioural development and are a risk factor for developing postpartum depression (7). Moreover, women struggling with infertility have higher levels of general anxiety and psychological stress than women who conceived naturally, around the time of the first trimester screening (8). As

prenatal invasive testing increases maternal anxiety, the invasive testing risks need to be thoroughly discussed with the mother. Some minor complications, such as cramping, vaginal spotting and pain after the procedure, and minimal amniotic fluid leakage, can occur. In our case, similar percentages of minor complications were observed in both groups: 75 AC cases (3.7%) and 29 CVS cases (3.8%). Women who experience leakage of amniotic fluid may have further risk of infection, premature rupture of membranes, foetal compromise (due to cord compression) and preterm delivery. These complications were observed in both groups. The risk of pregnancy loss increases with multiple attempts, with the presence of blood-stained amniotic fluid or foetal abnormalities. The risk of procedure-related pregnancy loss can be lowered with experience and familiarity with the procedure by the performing doctor (9). All the procedures in our facility were performed by expert personnel.

The most common indication for AC and CVS is still advanced maternal age, followed by a positive screening test in the first or second trimester. Unfortunately, data for the matched group on the background risk was not available from the National Institute of Public Health. We recognise this as a limitation of our study. Although the data for pregnancy loss in the matched group was carefully adjusted and compared in terms of gestation (weeks 11–14 for CVS and >15 week for AC), other data could not be obtained. There may therefore be more factors influencing our results from the matched group that remain unknown (such as maternal age, parity, history of pregnancy loss, chromosomal abnormalities).

Miscarriage is the most common complication in pregnancy. At least 25% of all women experience one or more sporadic miscarriages, usually due to random foetal chromosomal abnormalities, and this risk rises with increasing maternal age. The risk of foetal loss increases steeply after the age of 35, rising from 9% at 20–24 years to 75% at 45 years and older) (10). In our population, there was a high number of mothers with advanced maternal age as an indication for the procedure: 290 (35%) for CVS and 1,308 (60.4%) for AC. Another important predictive factor for pregnancy outcome is reproductive history. There was a lower number of primiparae in both the AC (536, 24.8%) and CVS (207, 25.0%) groups. Primiparae and women with a history of live births have a lower risk of miscarriage in their next pregnancy than women whose most recent pregnancy ended in miscarriage (10). In fact, more than 40% of women from both the AC and CVS groups had a history of one miscarriage or more.

The reason why the procedure-related risk of pregnancy loss was lower than expected in a comparable group of women who did not undergo the invasive procedure can be attributed to the relatively small number of cases. Because of the lack of a nationwide database, pregnancy outcome for all women who underwent the procedure could not be obtained. Moreover, 177 (5.9%) women were unreachable (wrong phone number, unanswered calls, moved abroad). Only 17 women (0.6%) who responded did not wish to participate in the study. The missing data represents a limitation to our study, as some pregnancy losses may not be recorded.

The emotional involvement of women with complications or abnormal karyotype analysis results could both be important reasons why they decline to take part. However, it is likely that women with complications would have been treated at our department and their data entered in the database. Unfortunately, data from other national hospitals and data on pregnancy losses in missing cases could not be obtained due to the patient privacy policy.

Women with indications for invasive procedures exhibit a higher risk of perinatal complications, which makes it hard to determine which of them are procedure-related. The procedures were performed by experienced operators, which is also an important factor in the procedure-related loss rate (3).

It may be that the risks were unrelated to the invasive procedure, and may reflect the pregnancy characteristics of women undergoing invasive testing. Ogilvie (11) similarly concluded that operator-specific risks were found to be more appropriate, and women should be counselled to understand that miscarriage risk following an invasive procedure is very low and that any pregnancy loss is likely to be due to other pregnancy-related and maternal factors.

A Cochrane review discovered that there were more spontaneous miscarriages after early AC compared with transabdominal CVS. However, there were no clear differences in pregnancy losses or anomalies (12).

Various authors (13, 14) have evaluated the postprocedural miscarriage rate after CVS and AC at different time intervals (intended and procedure-related losses within 2, 4, 6 and 10 weeks, or total miscarriage at <24 weeks) (15). In our study, we evaluated all pregnancy losses in a four-week period after the procedure. This time frame was decided arbitrarily and may not include all procedure-related miscarriages that could occur after the established interval. This is further limit of our study. However, one should note that it is estimated that about 25% of trisomy 21 foetuses are lost during pregnancy, and 40% of such losses occur by 24 weeks. Loss rates are even higher for other chromosomal anomalies, such as trisomies 13 and 18 and Turner syndrome (16). Consequently, not all miscarriages in pregnancies with chromosomal anomalies can be directly related to invasive prenatal testing.

The question that arises with the appearance and widespread use of non-invasive prenatal testing (NIPT) for karyotype analysis that carry no pregnancy risks is whether invasive tests are still justifiable. We have

to emphasise that NIPT is still a screening test (albeit with a very high sensitivity and specificity), while CVS and AC are diagnostic. NIPT measures the underlying genetic pathology of trisomies directly by analysing foetal genetic material in the maternal blood (cell-free foetal DNA, cffDNA). Several commercial testing strategies are available using different sequencing techniques for the screening of trisomy 21, 18 and 13 (17). The inclusion of NIPT in the prenatal programme lowers the number of unnecessary invasive procedures (18). While universal NIPT is not cost-effective, using NIPT contingently in women found at moderate or high risk by conventional screening is cost-effective. Positive NIPT results must still be confirmed using invasive techniques. Established screening, foetal ultrasound and invasive procedures with microarray testing allow the detection of a broad range of additional abnormalities not yet detectable by NIPT (19). Today, adequate prenatal counselling poses a substantial challenge given the broad range of prenatal testing options now available, and NIPT has the potential to improve pregnant women's experience of prenatal testing. All of the options should be carefully explained to pregnant women during the counselling procedure.

5 CONCLUSIONS

Our observation that procedure-related pregnancy loss rate is below 0.5% for AC and CVS merits consideration and accords with the results from recently published studies. We can be confident that invasive procedures in experienced perinatology centres are safe and that our data can be used for the counselling of patients before invasive procedures, when indicated.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

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