Procedure-Related Complications after Genetic Amniocentesis and Chorionic Villus Sampling

Komplikationen nach genetischer Amniozentese und Chorionzottenbiopsie

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Zusammenfassung

Ziel: Invasive pränatale Untersuchungen, wie Amniozentese (AC) und Chorionzottenbiopsie (CVS), spielen eine entscheidende Rolle in der Diagnostik genetischer Anomalien. Ziel der vorliegenden Studie ist die Ermittlung repräsentativer Zahlen über die Komplikationen nach genetischen Eingriffen in einem Tertiärzentrum.

Material und Methoden: In einer retrospektiven Analyse wurde das Outcome der an der Universitätsklinik für Frauenheilkunde und Geburtshilfe in Graz zwischen 2003 und 2010 betreuten Einlingsschwangerschaften, bei denen eine genetische AC oder CVS durchgeführt wurde, evaluiert. Primäres Outcome war das Auftreten einer Fehlgeburt oder eines Blasensprungs nach einem invasiven Eingriff.

Ergebnisse: Von den 1569 AC und 334 CVS (234 transabdominal, 99 transzervikal, 1 mit undokumentiertem Zugang) wurden 57 Fälle wegen schwerer kongenitaler Anomalien ausgeschlossen. Vollständige Daten konnten in 93,17 % erhoben werden. In 164 (8,89 %) Fällen wurde wegen genetischer oder struktureller Fehlbildungen ein Schwangerschaftsabbruch durchgeführt. Im restlichen Kollektiv kam es in 10 von 1342 (0,75 %) AC, 3 von 150 (2,00 %) transabdominalen CVS und 2 von 64 (3,13 %) transzervikalen CVS zu Komplikationen, die zu einer Fehlgeburt vor 24 SSW (n = 13) oder einem vorzeitigen Blasensprung (n = 2) innerhalb von 2 Wochen nach dem Eingriff führten. Die Komplikationsraten nach CVS waren höher als nach AC (OR 3,19).

Schlussfolgerung: Über einen 7-jährigen Beobachtungszeitraum betrugen die Komplikationsraten nach AC, transabdominaler und transzervikaler CVS 0,75 %, 2,00 % und 3,13 %. Dies ist vergleichbar mit neueren internationalen Untersuchungen.

Abstract

Purpose: Amniocentesis (AC) and chorionic villus sampling (CVS) play an important role in the diagnosis of genetic anomalies. The aim of this study was to evaluate presentable numbers of procedure-related complications of genetic interventions in a tertiary referral hospital.

Materials and Methods: The pregnancy outcome of women who underwent genetic AC or CVS during 2003 – 2010 at the Department of Obstetrics and Gynecology, Medical University of Graz, Austria, was analyzed retrospectively. The primary outcome was miscarriage or membrane rupture after an invasive procedure. Only singleton gestations were included.

Results: 1,569 AC procedures and 334 CVS procedures (234 transabdominal, 99 transcervical, 1 with undocumented route) were performed. Of these, 57 cases were excluded from further analysis because of severe anomalies. Complete outcome data were available for 93.17 % of cases. In 164 (8.89 %) cases the pregnancy was terminated due to genetic anomalies or severe malformations. In the remaining collective 10 of 1,342 (0.75 %) AC procedures, 3 of 150 (2.00 %) transabdominal CVS procedures and 2 of 64 (3.13 %) transcervical CVS procedures lead to complications resulting in miscarriage < 24 weeks (n = 13) or rupture of membranes (n = 2) within 2 weeks after procedure. Complication rates were significantly higher after CVS than after AC (OR 3.19).

Conclusion: Over an observation period of seven years, the complication rates after AC, transabdominal CVS and transcervical CVS were 0.75 %, 2.00 % and 3.13 %, respectively. These results are comparable to recent international investigations.

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Introduction

Since the introduction of first-trimester screening for chromosomal anomalies [1], the total number of invasive procedures has decreased due to better case selection [2, 3]. However, amniocentesis (AC), which was established more than 40 years ago [4], and chorionic villus sampling (CVS), which was first described in 1968 [5], still play an important role in the prenatal diagnosis of genetic anomalies. The risk of fetal loss following invasive procedures has been investigated in various studies and has been reported to be around 1.0 % for AC and somewhat higher for CVS, especially when performed transcervically [6 – 8]. However, the spontaneous fetal loss rate prior to 24 weeks of gestation without preceding procedure has been reported to be up to 1.0 % as well [6, 9 – 15]. In the past, AC and CVS have frequently been performed in women aged 35 years or older, or in those with an increased risk for chromosomal abnormalities, while invasive testing is currently mainly based on combined first-trimester risk assessment, which should be offered to all pregnant women [16, 17]. However, when counseling patients about procedure-related complications, physicians should refer to realistic numbers, according to their own experience which might be dependent on case load [16].

The aim of our study was therefore to evaluate presentable numbers of procedure-related complications of genetic procedures in a tertiary referral hospital with about 250 procedures per year.

Methods

We performed a retrospective study on pregnancy outcome in women with singleton gestation undergoing genetic AC or CVS between March 2003 and December 2010 at the Department of Obstetrics and Gynecology of the Medical University Graz, Austria. The study was approved by the local ethics committee (no.: 23-060 ex 10/11). Information about procedure-related complications was retrieved from the local electronic perinatal database (PIA, ViewPoint, GE Healthcare, Zipf, Austria) and the medical documentation system or patient files. In cases with missing outcome data, patients were contacted by phone. The indications for invasive prenatal diagnosis were maternal age ≥ 35 years, hereditary disease in the family, prior pregnancy with chromosome abnormality, conspicuous ultrasound or – increasingly – abnormal combined first-trimester screening. Cases with severe structural, genetic or functional anomalies of the fetus were retrospectively excluded from further analysis, due to their increased risk for spontaneous miscarriage or intrauterine death. All invasive procedures were performed under ultrasound guidance by trained specialists. Postprocedural complications were defined as fetal loss ≤ 24 weeks of gestation or rupture of membranes within 2 weeks after puncture. A secondary outcome was preterm delivery < 37 weeks of gestation.

Statistical analyses were performed with SPSS 19 (SPSS, Chicago, IL, USA) using a significance level of $\alpha = 0.05$. Categorical variables were analyzed by the Fisher's exact test or the Fisher-Freeman-Halton test. Results are presented as odds ratios with a 95 % confidence interval (95 % CI).

Results

Over an observation period of 7 years 1,903 invasive genetic procedures, i. e., 1,569 AC procedures and 334 CVS procedures, were performed in singleton pregnancies. The mean patient age was 36 years (range: 16 – 51) in the AC group and 34 years (range: 16 – 47) in the CVS group. The mean gestational age at the time of the procedure was 17.02 weeks (range: 14 – 34) in the AC group and 13.06 weeks (range: 11 – 17) in the CVS group. Of 334 CVS procedures, 234 (70.06 %) were carried out transabdominally, 99 (29.64 %) transcervically and in 1 case the route was not documented. In the majority of cases a 22-gauge needle (94.5 %) was used for AC, a 20-gauge (70.05 %) or 18-gauge needle (14.75 %) for transabdominal CVS and 2.0 mm forceps or catheter (Heintel Medizintechnik, Vienna, Austria) for transcervical CVS. Multiple insertions were required in 2.74 % of cases in the AC group, in 18.38 % of cases in the transabdominal CVS group and in 35.35 % of cases in the transcervical CVS group. There was no statistical difference in outcome between cases with multiple insertions compared to those with single insertion. Antibiotic prophylaxis was not part of the routine protocol. Fetal anomalies were detected in 159 (10.13 %) cases in the AC group (41.51 % structural malformations vs. 58.49 % genetic anomalies) and in 98 (29.34 %) cases in the CVS group (25.51 % structural malformations vs. 74.49 % genetic anomalies). In 164 (8.89 %) cases (84 [5.50 %] after AC, 80 [25.24 %] after CVS), the pregnancy was terminated upon parent request due to genetic anomalies or severe malformations. 57 fetuses (41 [2.61 %] in the AC group and 16 [4.79 %] in the CVS group) had severe structural, genetic or functional anomalies with increased risk for spontaneous miscarriage and intrauterine death and were therefore excluded from further analysis (**Table 1**). Sufficient outcome data were missing in 102 (6.68 %) cases in the AC group, 14 (6.31 %) in the transabdominal CVS group and 9 (9.47 %) in the transcervical CVS group leaving a final study population of 1,342, 150 and 64 cases, respectively. Complications resulting in miscarriage prior to 24 weeks of gestation, occurred in 9 (0.67 %) cases after AC, 3 (2.00 %) after transabdominal CVS and 1 (1.56 %) after transcervical CVS. Another two complications, one rupture of the membranes after AC (with subsequent uneventful delivery at 40 weeks) and one after transcervical CVS occurred within 2 weeks after the procedure, leading to final complication rates of 0.75 %, 2.00 % and 3.13 % for AC, transabdominal CVS and transcervical CVS, respectively (**Fig. 1**). Statistical analyses revealed that procedure-related complications occurred more frequently after CVS than after AC ($p = 0.0439$, OR 3.19, 95 % CI 1,078 – 9,418) and the outcomes after individual procedures differed significantly ($p = 0.0449$, Fisher-Freeman-Halton test). How-

Table 1 Numbers and reasons for exclusion (n = 57).

diagnosis	number of cases
trisomy 21	7
monosomy 45 X	7
cardiac malformations	7
cerebral malformations	6
trisomy 18	4
congenital diaphragmatic hernia	4
rupture of membranes before intervention	4
47 XXY	3
triploidy	3
severe intrauterine growth restriction	3
trisomy 13	2
trisomy 15	2
hygroma colli	2
hydrops fetalis	2
skeletal dysplasia	1

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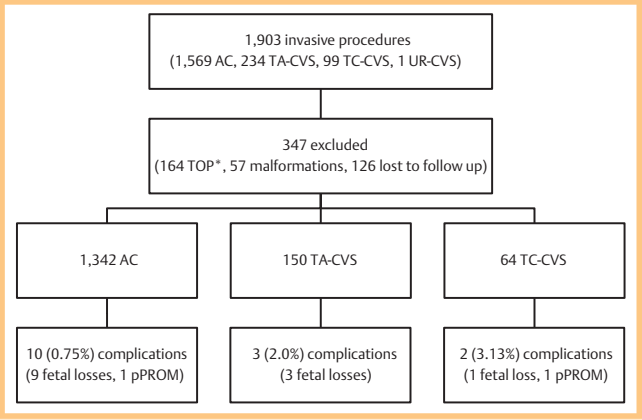

Fig. 1 Outcome of pregnancies following amniocentesis (AC), transabdominal (TA-CVS) and transcervical chorionic villus sampling (TC-CVS) and the respective procedure-related complications including preterm premature rupture of membranes (pPROM) and fetal loss. In one case of CVS, the route was not documented (UR-CVS). * TOP = termination of pregnancy.

Abb. 1 Schwangerschaftsoutcome nach Amniozentesen (AC), transabdominalen (TA-CVS) und transzervikalen Chorionzottenbiopsien (TC-CVS) sowie Auflistung der eingriffsbezogenen Komplikationen, wie vorzeitiger Blasensprung (pPROM) und Fehlgeburt. In einem Fall der CVS-Gruppe wurde der Zugangsweg nicht dokumentiert (UR-CVS). * TOP = Schwangerschaftsabbruch.

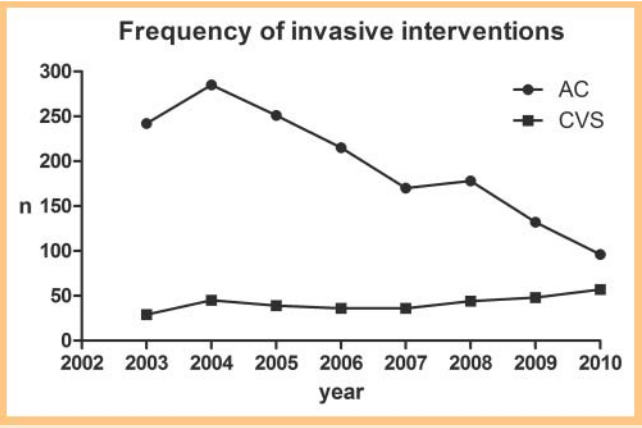

Fig. 2 Number of invasive genetic procedures per year from 2003 – 2010.

Abb. 2 Anzahl der invasiven genetischen Eingriffe pro Jahr zwischen 2003 und 2010.

ever, the numbers were obviously too small to result in significant differences in subgroup analyses.

Preterm delivery, defined as birth < 37 + 0 weeks of gestation occurred in 120 (8.94 %) pregnancies after AC, in 9 (6.00 %) after transabdominal CVS and in 8 (12.50 %) after transcervical CVS. Birth < 34 + 0 weeks of gestation was observed in 49 patients (3.65 %) after AC, 2 patients (1.33 %) after transabdominal CVS and 5 patients (7.81 %) after transcervical CVS. The overall preterm delivery rate (birth < 37 + 0 weeks of gestation) at our institution in the study period was 15.8 %.

Over the study period, the number of genetic AC procedures steadily declined while the number of CVS procedures increased slightly (**Fig. 2**).

Discussion

Over an observation period of seven years, there was an overall decline in invasive procedures that was caused by a decrease in the frequency of AC procedures while CVS rates increased slightly. This was most likely due to the better case selection for invasive testing by the increasing use of combined first-trimester screening in our institution and the local referring units. In the present study the complication rate after AC, including miscarriage as well as ruptured membranes, was 0.75 %. This result is comparable to recent reports and supports the safety of this diagnostic tool [6, 9 – 15, 18, 19].

Complications after CVS occurred more frequently, especially after the transcervical approach. The decision whether to undergo AC or CVS to detect genetic anomalies may be difficult to make and requires extensive counseling. The clear advantage of an early procedure is the avoidance of a prolonged period of uncertainty and the availability of less stressful procedures in cases in which termination of pregnancy is desired after an abnormal result. In many institutions risk assessment and invasive intervention can even be offered at the same visit ("one-stop clinic for assessment of risk" [OSCAR]) [20].

However, the disadvantage is the increased risk of miscarriage after CVS. Some authors even reported higher rates of limb reduction and subsequent development of preeclampsia, which recent reports could not confirm [21 – 24]. Several studies stated comparable miscarriage rates following AC and transabdominal CVS [7, 8, 25], while transcervical CVS seems to be associated with a higher risk of pregnancy loss [26], although the reported data for CVS vary significantly [27]. In the present study transcervical CVS seemed to cause more complications as well, suggesting that it might be better to avoid this technique. In cases of difficult abdominal access, the patient should be informed that it might be preferable to wait until an AC can be safely performed at an advanced gestational age. Although the frequency of multiple insertions appears to be quite high in our population, this did not have a significant impact on outcome. The higher frequency might be partly explained by the applied techniques especially in cases with transcervical CVS.

It is likely that the earlier gestational age for CVS constitutes an important contributing factor for the higher rate of complications after this intervention, since the fetal loss rate without any invasive procedure obviously decreases with advancing gestation. Prior to 24 weeks of gestation, it has been reported to be 0.4 – 1 % [6, 9 – 15], which has to be taken into account when interpreting complication rates. Since there is also an association with maternal age and the reason for the procedure [28], the background loss rate also depends on the individual patient population of a unit [28]. Our unit is a tertiary care referral center dealing with high risk pregnancies. Therefore, cases with associated anomalies being likely to increase the risk for miscarriage or intrauterine demise were excluded from the final analysis.

This study was not without limitations, since it was retrospectively designed and reports a single-center experience with limited case numbers, while the best study design to evaluate the procedure-related miscarriage rate would be a prospective, controlled trial of women included very early in pregnancy. Nonetheless, the presented results are important and can be used by clinicians in units with a comparable case load to inform patients, since physicians should generally refer to realistic complication rates and compare their own results with reported numbers from the literature [29, 30].

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References

1 *Spencer K*, *Souter V*, *Tul N et al.* A screening program for trisomy 21 at 10 – 14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999; 13: 231 – 237

2 *Tabor A*, *Vestergaard CH*, *Lidegaard O.* Fetal loss rate after chorionic villus sampling and amniocentesis: an 11-year national registry study. Ultrasound Obstet Gynecol 2009; 34: 19 – 24

3 *Hagen A*, *Entezami M*, *Gasiorek-Wiens A et al.* The impact of first trimester screening and early fetal anomaly scan on invasive testing rates in women with advanced maternal age. Ultraschall in Med 2011; 32: 302 – 306

4 *Jacobson CB*, *Barter RH*. Intrauterine diagnosis and management of genetic defects. Am J Obstet Gynecol 1967; 99: 796 – 807

5 *Hahnemann N*, *Mohr J.* Genetic diagnosis in the embryo by means of biopsy from extra-embryonic membrane. Bull Eur Soc Hum Genet 1968; 2: 23 – 29

6 *Tabor A*, *Philip J*, *Madsen M et al.* Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986; 1: 1287 – 1293

7 *Rhoads GG*, *Jackson LG*, *Schlesselman SE et al.* The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. N Engl J Med 1989; 320: 609 – 617

8 *Smidt-Jensen S*, *Permin M*, *Philip J et al.* Randomised comparison of amniocentesis and transabdominal and transcervical chorionic villus sampling. Lancet 1992; 340: 1237 – 1244

9 *Muller F*, *Thibaud D*, *Poloce F et al.* Risk of amniocentesis in women screened positive for Down syndrome with second trimester maternal serum markers. Prenat Diagn 2002; 22: 1036 – 1039

10 *Seeds JW*. Diagnostic mid trimester amniocentesis: how safe? Am J Obstet Gynecol 2004; 191: 607 – 615

11 *Kong CW*, *Leung TN*, *Leung TY et al.* Risk factors for procedure-related fetal losses after mid-trimester genetic amniocentesis. Prenat Diagn 2006; 26: 925 – 930

12 *Eddleman KA*, *Malone FD*, *Sullivan L et al.* Pregnancy loss rates after midtrimester amniocentesis. Obstet Gynecol 2006; 108: 1067 – 1072

13 *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

14 *Towner D*, *Currier RJ*, *Lorey FW et al.* Miscarriage risk from amniocentesis performed for abnormal maternal serum screening. Am J Obstet Gynecol 2007; 196: 608. e1 – e5

15 *Odibo AO*, *Gray DL*, *Dicke JM et al.* Revisiting the fetal loss rate after second-trimester genetic amniocentesis: a single center's 16-year experience. Obstet Gynecol 2008; 111: 589 – 595

16 *Nicolaides KH.* First-trimester screening for chromosomal abnormalities. Semin Perinatol 2005; 29: 190 – 194

17 *Luthgens K*, *Hoopmann M*, *Alkier R et al.* First-Trimester Screening for Trisomies 18 and 13 with the Combined Use of the Risk Algorithms for Trisomy 21, 18 and 13. Ultraschall in Med 2012, in press

18 ACOG Practice Bulletin No. 27: Clinical Management Guidelines for Obstetrician-Gynecologists. Prenatal diagnosis of fetal chromosomal abnormalities. Obstet Gynecol 2001; 97: S1 – S12

19 ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol 2007; 109: 217 – 227

20 *Bindra R*, *Heath V*, *Liao A et al.* One-stop clinic for assessment of risk for trisomy 21 at 11–14 weeks: a prospective study of 15 030 pregnancies. Ultrasound Obstet Gynecol 2002; 20: 219 – 225

21 *Philip J*, *Silver RK*, *Wilson RD et al.* Late first-trimester invasive prenatal diagnosis: results of an international randomized trial. Obstet Gynecol 2004; 103: 1164 – 1173

22 *Grobman WA*, *Auger M*, *Shulman LP et al.* The association between chorionic villus sampling and preeclampsia. Prenat Diagn 2009; 29: 800 – 803

23 *Khalil A*, *Akolekar R*, *Pandya P et al.* Chorionic villus sampling at 11 to 13 weeks of gestation and hypertensive disorders in pregnancy. Obstet Gynecol 2010; 116: 374 – 380

24 *Odibo AO*, *Singla A*, *Gray DL et al.* Is chorionic villus sampling associated with hypertensive disorders of pregnancy? Prenat Diagn 2010; 30: 9 – 13

25 *Alfirevic Z*, *Sundberg K*, *Brigham S.* Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2003; 3: CD003252

26 *Chueh JT*, *Goldberg JD*, *Wohlferd MM et al.* Comparison of transcervical and transabdominal chorionic villus sampling loss rates in nine thousand cases from a single center. Am J Obstet Gynecol 1995; 173: 1277 – 1282

27 *Mujezinovic F*, *Alfirevic Z.* Procedure-related complications of amniocentesis and chorionic villous sampling: a systematic review. Obstet Gynecol 2007; 110: 687 – 694

28 *Tabor A*, *Alfirevic Z.* Update on procedure-related risks for prenatal diagnosis techniques. Fetal Diagn Ther 2010; 27: 1 – 7

29 *Alfirevic Z.* Who should be allowed to perform amniocentesis and chorionic villus sampling? Ultrasound Obstet Gynecol 2009; 34: 12 – 13

30 *Agarwal K*, *Alfirevic Z.* Pregnancy Loss after Chorionic Villus Sampling and Genetic Amniocentesis in Twin Pregnancies – a Systematic Review. Ultrasound Obstet Gynecol 2011. DOI: 10.1002/uog.10152

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