CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

Safety of amniocentesis in normal pregnancies and pregnancies considered high-risk due to fetal genetic anomalies – an observational study

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Summary

Purpose: To evaluate the effect of clinical and demographic factors on the further course of pregnancy and post-procedure complications in healthy and high-risk pregnancies. *Materials and Methods:* Data of 230 amniocenteses with normal (n=174) and abnormal genetic findings (n=56) were collected retrospectively. Details of birth, neonatal condition, patient characteristics, and post-procedure complications were analysed. *Results:* The mean maternal age at amniocentesis was 34.50 ± 5 years-old. One hundred (43.48%) were followed by at least one complication. Fetal death occurred after 11 (4.78%) procedures including seven with genetic disorders. There was no significant difference in complication rates between study groups, except for fetal death, which was significantly more common in high-risk pregnancies ($p = 0.0017$). Abdominal pain correlated with pyrexia and vaginal bleeding. *Conclusion:* The most severe complications were associated with fetal genetic disorders. The authors conclude that amniocentesis is a safe procedure; however, significant correlations between the incidence of certain complications may be relevant in planning antenatal care.

Key words: Amniocentesis; Adverse effects; Congenital abnormalities; Prenatal care; Prenatal diagnosis.

Introduction

Early detection of fetal developmental abnormalities or health conditions enables optimal preventive and therapeutic management. Proper antenatal care and prenatal testing lead to the reduction of ante- and perinatal mortality. [1, 2] According to the guidelines published by the Polish Society of Gynecology, all pregnant women should be offered screening for the most common developmental abnormalities and chromosomal aberrations. If the results of screening suggest the presence of anomalies, invasive prenatal testing should be offered. Invasive tests can also be offered to pregnant women over 40 years of age, as well as to those who did not consent to screening [3]. Nicolaides *et al.* designate the period of 11 to 13 gestational weeks as the optimal window for prenatal screening, postulating that once the pregnancy is classified as low-risk, the number of follow-up tests can be significantly reduced [4].

Congenital defects and genetic disorders can occur in both high-risk and healthy pregnancies, hence the need to carry out screening in all women [3]. The estimated incidence of major genetic anomalies leading to developmental disorders is about 2-3% of all live births [5-7]. However, the total incidence of genetic aberrations is difficult to estimate, since most such fetuses, especially those with major anomalies, die early in pregnancy, and the preimplantation loss rates are completely unknown. As such, the incidence of fetal genetic disorders decreases with gestational age. Chromosomal aberrations are found in approximately 50% of spontaneously miscarried embryos, or approximately 2% of fetuses spontaneously miscarried at 16-18 gestational weeks, compared to only one in 160 living births [8, 9].

Amniocentesis with genetic testing remains the "gold standard" of invasive prenatal diagnosis, as it offers 100% sensitivity with low risk of complications. It is typically carried out in the second trimester. The amniotic membrane is punctured in an ultrasound-guided procedure to avoid injury to the placenta or fetus. Amniotic fluid sampling enables chromosomal analysis that can detect genetic disorders, congenital metabolic disorders, neural tube defects, abdominal wall defects, and haemolytic disease of the fetus and new-born, as well as to determine the sex of the fetus and fetal lung maturity [10]. The spontaneous miscarriage rate following amniocentesis is positively correlated with maternal age, number of punctures, presence of leiomyomas, and maternal obesity, and it is negatively correlated with operator experience [3, 11-13].

Amniocentesis is associated with a low risk of complications, estimated to be 0.5-1% [12, 14]. While spontaneous miscarriage is the most emotional of them, other maternal and fetal complications are also possible. Continuous assessment of potential risk factors affecting the mother and fetus with the analysis of complications of am-

Revised manuscript accepted for publication June 18, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 3, 2019
doi: 10.12891/ceog4713.2019

7847050 Canada Inc.
www.irog.net

Published: 10 June 2019

niocentesis, especially in pregnancies considered high risk due to fetal genetic disorders, can improve the standard of antenatal care. Therefore, the aim of this research was to evaluate the effect of a number of clinical and demographic factors on the further course of pregnancy and complications of amniocentesis in healthy pregnancies and pregnancies considered high risk due to fetal genetic anomalies.

Material and Methods

The authors analysed 230 amniocentesis procedures performed on 219 women from 2013 to 2015. The analysis included a retrospective review of patient medical records and postnatal survey data. The enrolled subjects were classified in one of two groups: pregnancy with normal genetic findings (n=174) and pregnancy with abnormal genetic findings (n=56). Additionally, they assessed the effect of gestational age at amniocentesis on complication rates. The study protocol was reviewed and approved by the Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki. Each enrolled patient gave her written informed consent to participate in the study.

The following data was sourced from the patients' medical records: gravidity and parity, procedure details, maternal clinical condition before and directly after amniocentesis, as well as post-procedure complications and symptoms. Details of birth and neonatal condition were sourced from the postnatal survey.

The data are presented as means (SD) and percentages. The data were analysed for normality using the Kolmogorov-Smirnov test with Lilliefors correction. For comparison between groups, the Chi-squared test was used for categorical data and the Mann-Whitney U test for quantitative variables was used. Spearman's correlation rank was used to determine the correlations between the variables. All data were analysed statistically using the Statistica software package, v10. A of $p < 0.05$ value was considered statistically significant for all comparisons.

Results

The mean maternal age was 34.50 ± 5 (range: 22 to 47) years. Amniocentesis was performed at 12 to 24 gestational (mean of 16.13 ± 2.02) weeks. Early amniocentesis (i.e. by the end of 15th gestational week) was performed in 111 (48%) women, whereas the remaining 119 (52%) procedures were performed at 16 or more gestational weeks. A high percentage of early amniocenteses was due to retrospective study design and previous practices at the institution.

Most women in the present study group were primigravidae and secundigravidae (n=171), with only 44 tertigravidae. Other multigravidae (quadri- and quinti-) constituted a small ratio of the study group. The mean gravidity was 1.93 ± 0.96. Two hundred eight (94.43%) of 230 amniocenteses were performed in naturally conceived pregnancies. In this subgroup, amniocentesis had to be repeated in three women, while four other women had twin pregnancy. The mean age of women with normal pregnancy was 34.34 ± 4.23 years-old; amniocentesis was performed in this group at the mean gestational age of 16.18 ± 2.14 weeks. The mean age of patients with pregnancy considered high risk due to a confirmed foetal genetic disorder was 34.34 ± 5.22 years-old; amniocentesis was performed in this group at the mean gestational age of 16.11 ± 1.98 weeks.

The mean gestational age at birth was 34.57 ± 7.96 (range of 13 to 42) weeks. The women from the present study group had either vaginal or caesarean delivery. Of 66 vaginal deliveries, labour started with the rupture of membranes in 21 and with regular uterine contractions in 45. Seven neonates with genetic anomalies had Apgar scores of zero to seven. Caesarean sections were performed in 125 cases, with 85 procedures scheduled in advance.

Fetal abnormalities were confirmed in 56 women with abnormal amniocentesis findings. The most common anomaly (22 cases) was Down syndrome (Trisomy 21). It was concomitant with congenital heart defect in two cases, and in one case with Klinefelter syndrome, an exceptionally rare comorbidity of Down syndrome. Multiple fetal anomalies were found in two cases. There were also six cases of Edwards syndrome and six cases of Turner syndrome. The remaining cases included less common genetic anomalies.

Of 230 amniocenteses performed, 100 (43.48%) were followed by at least one complication and 130 (56.52%) were uneventful. The most severe complication, intrauterine fetal death, occurred after 11 (4.78%) procedures. Seven of these cases were associated with a fetal genetic disorder. In two cases, there was no evident cause of death and the fetal karyotype was normal. There was also one case of oligohydramnios followed by anhydramnios. The last case was a late fetal death at 34 gestational weeks, due to placental insufficiency and several placental infarctions. There was no significant difference in complication rates between normal and high-risk pregnancy groups, except for post-procedure fetal death, which was significantly more common in high-risk pregnancies ($p = 0.0017$). Table 1 shows the incidence of complications of amniocentesis.

The evaluation of the cause-and-effect relationship between amniocentesis and fetal death showed that 16 of 20 pregnancies lost within two weeks of the performed amniocentesis were terminated upon maternal request due to a severe and irreversible foetal anomaly. Four remaining cases of spontaneous loss were associated with Edwards syndrome, fragile X syndrome, Down syndrome with concomitant heart defects, and stand-alone Down syndrome. In the normal pregnancy group, there was only a single case (0.6%) of intrauterine fetal death within 14 days of the procedure. The patient reported malaise, nausea, and headache on the fourth day following amniocentesis, with an ultrasound performed on day 14 showing an undetectable fetal heart rate. Other cases of intrauterine fetal death occurred more than two weeks after amniocentesis (due to placental insufficiency or without any evident cause of death).

There was a significant correlation between the presence of anomalies and the incidence of anomaly-related complications, for example gestational age at birth, APGAR score

Table 1. — *Complications following the amniocentesis procedure in normal pregnancies and pregnancies considered high-risk due to a fetal genetic abnormality.*

Factor	Normal pregnancies (n=174)	High-risk pregnancies (n=56)	*p* value
1. Abdominal pain/uterine contractions [b]	3.39 (1.48)	2.95 (1.29)	0.8794
2. Pain [a]			
No	144 (62.61%)	49 (21.30%)	0.4009
Yes	30 (13.04%)	7 (3.04%)	
3. Pyrexia * [a]			
No	172 (74.78%)	53 (23.04%)	0.0604
Yes	2 (0.87%)	3 (1.30%)	
4. Dizziness/syncope * [a]			
No	167 (72.61%)	54 (23.48%)	0.8795
Yes	7 (3.04%)	2 (0.87%)	
5. Amniotic fluid leakage * [a]			
No	172 (74.78%)	53 (23.04%)	0.0604
Yes	2 (0.87%)	3 (1.30%)	
6. Vaginal bleeding * [a]			
No	172 (74.78%)	55 (23.91%)	0.7151
Yes	2 (0.87%)	1 (0.43%)	
7. Fetal death * [a]			
No	170 (73.91%)	49 (21.30%)	0.0017
Yes	4 (1.74%)	7 (3.04%)	

[a] *Chi-squared test (number of subjects; percentage);* [b]*Mann-Whitney U test (mean; standard deviation)*

or fetal death. However, there was no significant correlation between the presence of anomalies and maternal clinical characteristics. Early amniocentesis was performed more often in women who conceived after assisted reproductive technology (10.81% *vs.* 8.40%; $p = 0.0327$). There were differences in gestational age at birth (33.53 *vs.* 35.31; $p = 0.0267$) and the rate of caesarean delivery (53.15% *vs.* 53.78%; $p = 0.8472$) between the groups after early and mid-trimester amniocentesis. In women after early amniocentesis, labour more frequently started with the rupture of membranes (10.81% *vs.* 7.56%; $p = 0.8540$), whereas in women after mid-trimester amniocentesis, it tended to start with regular uterine contractions (11.71 *vs.* 26.89%; $p = 0.0079$). There were significant correlations between post-procedure complications, which may signify maternal or fetal distress, for example between abdominal pain/uterine contractions and the severity of generalized pain ($r = 0.58$), pyrexia ($r = 0.014$), and vaginal bleeding ($r = 0.18$), as well as between pyrexia, fetal death ($r = 0.20$), and abdominal pain/uterine contractions ($r = 0.14$). Table 2 shows inter-variable correlation coefficients.

Discussion

Invasive prenatal testing is an emotional topic for pregnant women, due to possible complications. The present study shows that amniocentesis is a safe procedure in both healthy pregnancies and pregnancies considered high risk due to a fetal genetic disorders. Complication monitoring is crucial to ensure a high quality of antenatal care, and continuous improvement of screening tests aims to decrease the number of invasive procedures. The ultimate goal is to develop 100% safe, non-invasive diagnostic tests capable of detecting the most common lethal fetal anomalies and congenital defects [15, 16]. Currently, though, invasive tests are the key to prenatal diagnosis, and doctors are obligated to ensure their safest possible execution [3, 10, 17, 18].

Complication analysis is an integral part of assessing the safety of any medical procedure. The increasing number of performed amniocentesis procedures makes it even more essential to continuously assess the procedure's safety in different patient populations. Fetal chromosomal aberrations were confirmed in almost a quarter of assessed pregnancies (24.66%), which is why the study sample has been divided into two groups: normal pregnancy (fetal genetic disorder-free) and high-risk pregnancy (with a confirmed fetal genetic disorder). In the normal pregnancy group, there was only a single case (0.6%) of the most severe complication of amniocentesis, i.e., intrauterine fetal death within 14 days after the procedure. It is lower than has been reported in the literature. The CEMAT study demonstrated a post-procedure spontaneous loss rate of 2.6% for early amniocentesis and of 0.8% for mid-trimester amniocentesis [19], whereas an analysis of over 68,000 pregnancies from a number of clinical studies demonstrated a post-procedure spontaneous loss rate of 0.33% [20]. The miscarriage rate following amniocentesis is positively correlated with maternal age, number of punctures, presence of leiomyomas, and maternal obesity, and it is negatively correlated with the operator's experience [3, 11-13]. Attempts have also been made to limit side effects causing patient discomfort during amniocentesis, such as pain or bleeding [21-23]. The present study was conducted in a tertiary re-

Table 2. — *Correlations between study parameters.*

Variable	Maternal age	Gestational age at amniocentesis	Gravidity	Abdominal pain/ uterine contractions	Gestational age at birth	APGAR score at 1 min.	Pain	Pyrexia	Dizziness/syncope	Rupture of membranes	Vaginal bleeding	Post-procedure fetal death	ART	Cesarean delivery	Genetic anomaly
Maternal age at childbirth	1.00	-0.06	**0.31**	**-0.13**	-0.01	0.08	-0.08	0.10	0.01	0.08	0.04	0.03	0.07	0.09	0.05
Gestational age at amniocentesis	-0.06	1.00	0.08	-0.10	**0.14**	0.00	-0.10	**-0.15**	-0.03	-0.09	-0.09	-0.04	-0.06	0.02	-0.05
Gravidity	**0.31**	0.08	1.00	-0.02	0.02	0.09	-0.04	-0.05	-0.09	-0.09	0.02	0.02	**-0.15**	-0.03	-0.02
Abdominal pain/ uterine contractions	**-0.13**	-0.10	-0.02	1.00	0.05	-0.02	**0.58**	**0.14**	**0.17**	0.07	**0.18**	0.05	-0.01	-0.06	-0.04
Gestational age at birth	-0.01	**0.14**	0.02	0.05	1.00	**0.67**	0.00	**-0.13**	0.04	**-0.15**	0.04	**-0.31**	**-0.17**	**0.28**	**-0.59**
APGAR score at 1 min.	0.08	0.00	0.09	-0.02	**0.67**	1.00	-0.06	**-0.15**	-0.02	-0.11	-0.02	**-0.33**	0.03	**0.38**	**-0.71**
Pain	-0.08	-0.10	-0.04	**0.58**	0.00	-0.06	1.00	0.02	**0.22**	0.02	**0.16**	0.01	-0.06	-0.02	-0.06
Pyrexia	0.10	**-0.15**	-0.05	**0.14**	**-0.13**	**-0.15**	0.02	1.00	-0.03	**0.39**	-0.02	0.11	**0.15**	-0.10	0.12
Dizziness/syncope	0.01	-0.03	-0.09	**0.17**	0.04	-0.02	**0.22**	-0.03	1.00	0.12	-0.02	-0.05	0.01	0.05	-0.01
Amniotic fluid leakage	0.08	-0.09	-0.09	0.07	**-0.15**	-0.11	0.02	**0.39**	0.12	1.00	-0.02	-0.03	**0.15**	-0.04	0.12
Vaginal bleeding	0.04	-0.09	0.02	**0.18**	0.04	-0.02	**0.16**	-0.02	-0.02	-0.02	1.00	-0.03	-0.04	0.11	0.02
Post-procedure fetal death	0.03	-0.04	0.02	0.05	**-0.31**	**-0.33**	0.01	0.11	-0.05	-0.03	-0.03	1.00	-0.07	**-0.24**	**0.21**
ART	0.07	-0.06	**-0.15**	-0.01	**-0.17**	0.03	-0.06	**0.15**	0.01	**0.15**	-0.04	-0.07	1.00	**0.16**	-0.05
Cesarean delivery	0.09	0.02	-0.03	-0.06	**0.28**	**0.38**	-0.02	-0.10	0.05	-0.04	0.11	**-0.24**	**0.16**	1.00	**-0.38**
Fetal anomaly	0.04	-0.03	-0.01	-0.05	**-0.55**	**-0.68**	-0.08	0.10	-0.02	0.12	0.04	**0.20**	-0.06	**-0.35**	**0.99**

ART: assisted reproductive technology. Significant correlations marked in bold.

ferral hospital, where the staff are experienced in performing amniocentesis and providing antenatal care for high-risk pregnancies, which improves the safety of the procedure.

With the advent of ultrasound-guided amniocentesis, the overall complication rate decreased from 2.1% to 1.4%. Injury to the fetus (such as skin scars, eye injury, or subarachnoid hematoma) is another potential complication of amniocentesis caused directly by the needle. Obstetric complications such as vaginal bleeding or amniotic fluid leakage are so rare that it is difficult to estimate their incidence. [20] Neonates exposed to genetic amniocentesis have an increased risk of respiratory distress syndrome and pneumonia [14]. In terms of fetal developmental abnormalities, congenital talipes equinovarus was reported significantly more often after early amniocentesis (1.3% *vs.* 0.1%) [19, 24]. However, in the present study sample, the authors did not observe this congenital abnormality.

From a clinical perspective, the observed correlations between different post-procedure complications appear interesting, as the presence of one complication may be considered a predisposing factor or a red flag for the onset of another one. However, the literature review did not yield a large number of studies assessing intervariable correlations between the individual complications of amniocentesis. Although the CEMAT study did not demonstrate a significant difference in amniotic fluid leakage after early and mid-trimester amniocentesis, post-procedure amniotic fluid leakage increased the risk of congenital talipes equinovarus in neonates [19]. Johnson *et al.* named three factors associated with the increased risk of spontaneous miscarriage after early amniocentesis. Each of them alone increases the risk of pregnancy loss several-fold. These were procedures 'judged to be difficult' by the operator (5.73% *vs.* 2.45%; $p = 0.001$), post-procedure amniotic fluid leakage (11.7% *vs* 2.4%; $p = 0.001$), and bleeding (10.5% *vs.* 2.1%; $p = 0.001$) [25].

The present analysis showed that some complications co-occur significantly more often. There was a significant correlation between the presence of abdominal pain/uterine contractions and the severity of generalized pain ($r = 0.58$), pyrexia ($r = 0.14$), and vaginal bleeding ($r = 0.18$). There was a significant positive correlation between pyrexia and intrauterine fetal death ($r = 0.20$), as well as the presence of abdominal pain/uterine contractions ($r = 0.14$). However, there was no significant correlation between the presence of fetal chromosomal aberration and the incidence of post-procedure complications. The obtained results appear interesting. They emphasize the need to carefully monitor those women who present with even the mildest post-procedure complications, especially pyrexia, which seems to be the most severe complication. However, due to relatively low complication rates in the present study group, further research is necessary.

When discussing type of birth, it is important to consider women's motivation and their attitudes to vaginal or caesarean delivery. In their survey study of a thousand women, Torloni *et al.* demonstrated that 20% of women preferred caesarean delivery. These were mainly younger women with either vocational qualifications or university degrees,

usually primigravidae. They preferred caesarean delivery due to fear of pain (77%) and the comfort of having a planned delivery (74%). Most women in this group (64%) expressed the view that this type of delivery is safer for the mother and less traumatic for the new-born [26]. Newborn safety is a key issue, especially in high-risk pregnancies, and the present results confirm this conclusion. Correlation analysis demonstrated a significant positive association between caesarean delivery and assisted reproductive technology.

There was a high rate of fetuses with genetic anomalies in the present sample. It should be noted, though, that the study group was recruited from women receiving antenatal care in the tertiary referral hospital, which typically manages higher-risk pregnancies than primary or secondary referral centres, and often for mothers with pre-existent systemic diseases, which may adversely affect the course of pregnancy.

Amniocentesis is a safe procedure in healthy pregnancies. The most severe complication of amniocentesis, for example intrauterine fetal death up to 14 days following amniocentesis, occurred significantly more frequently in pregnancies with a confirmed fetal genetic disorder than in those with a normal fetal karyotype. There were some significant correlations between the incidence of certain complications that may be relevant in planning antenatal care; however, more research in larger patient samples is needed to clarify them further.

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