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Fetal loss after amniocentesis: analysis of a single center's 7,957 cases in China

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Summary

Purpose of investigation: The fetal loss rate after amniocentesis was different in previous reports. Instead of using the fetal loss rate reported by others when facing the counseling couples, the present authors sought to estimate our institution-specific fetal loss rate after amniocentesis. *Materials and Methods:* The study included 7,957 Chinese women in singleton pregnancy that had an amniocentesis in mid-trimester between 18-26 weeks of gestation in Shengjing Hospital for any indication. All clinical data, fetal karyotype, and pregnancy outcome were collected for analysis in the present study. *Results:* The number of abnormal karyotypes detected in this study were 436 (5.48%). The loss follow-up rate was 0.45%. The total fetal loss rate after amniocentesis was 4.09 % including 3.23% elective termination of pregnancy and 0.86% unintended fetal loss. The potentially procedure-related fetal loss rate was lower than 0.59%. The potentially procedure-related fetal loss rate was found to be significantly associated with maternal age (> 35 years), previous fetal loss history, and abnormal vaginal bleeding in this pregnancy. *Conclusion:* 5.48% of women with amniocentesis have abnormal karyotypes and the proportion of women with major chromosomal abnormalities was even 2.20%; on the contrary, the fetal loss rate related to the procedure was lower than 0.59%.

Key words: Amniocentesis; Abnormal karyotypes; Fetal loss.

Introduction

Amniocentesis was first introduced in the 1950s for sex determination, and was applied in clinical practice in 1966 to obtain fetal cells for karyotyping [1]. Now amniocentesis is an invasive prenatal diagnostic examination widely performed for screening fetal karyotypic abnormalities early in the second trimester of pregnancy in clinical practice. Before amniocentesis, as with any procedure, informed consent must include a complete and accurate discussion. The counseling discussion includes the risks of the procedure, the limitations, and accuracy of the laboratory testing, the risk and burden of the disease(s) that might be diagnosed, the utility of the diagnostic information, and the fetal loss. In the end the couples' decision depends on simply the outcomes: the risk of having a child with a chromosomal abnormality or a specific genetic disease compared with the risk of losing a normal pregnancy as a result of the procedure.

The incidence of pregnancy loss following mid-trimester amniocentesis has traditionally been estimated to be 0.5%, which is based on recommendations by the Centers for Disease Control and Prevention (CDC) and endorsed by the American College of Obstetricians and Gynecologists (ACOG) [2,3]. During two past decades, advances in ultrasound imaging technology and developments in molecular biology have led to an increase in new indications for amniocentesis. The loss rates reported in these more recent studies [4, 5] are different from those reported in previous reports [6, 7]. There is a wide variation in the reported incidences regarding the fetal loss rate after amniocentesis.It ranges form 0.06% [4] to 1.4% [8]. Comparing rates between these studies is difficult because of their differences relative to exclusion criteria, gestational age range at amniocentesis, and follow-up period used to calculate fetal loss rates. Instead of using the fetal loss rate reported by others when facing the counseling couples, the present authors sought to estimate their institution-specific fetal loss rate after amniocentesis.

Materials and Methods

To estimate the present institution-specific fetal loss rate, the present authors collected the data of 7,957 Chinese women in singleton pregnancy who had mid-trimester amniocentesis between 18-26 weeks of gestation in Shengjing Hospital of China Medical University between January 2007 and December 2011. They excluded all second amniocenteses, for any reason. The research protocol was approved by the ethics committee of the Shengjing Hospital of China Medical University. All pregnant women who had amniocentesis indications were referred to the obstetric clinic for further counseling. At the time of counseling all referred patients received an ultrasound examination to confirm gestational age. An amniocentesis was arranged for those women who elected to have the procedure after the procedure itself and related risks were thoroughly explained to the couple and written consent was obtained in all cases.

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Table 1. — *The indications for amniocentesis.*

Indications	n	%
Increased risk of serum biochemical screening for Down syndrome (> 1/270)	3,677	46.21
Advanced maternal age (> 35 years)	2,662	33.45
Previous abnormal baby history	779	9.79
Positive sonographic markers for aneuploidies	343	4.31
Maternal anxiety	236	2.97
Drug use and environmental factor	166	2.09
Abnormal karyotype in either of couples	67	0.84
Consanguineous marriage	27	0.34
Total amniocentesis	7,957	100

Amniocentesis was usually arranged to be performed for all cases in mid-trimester between 18-26 weeks of gestation. Six senior operators used the same facilities and had the same objectives. Amniocentesis was performed with a 22-gauge needle as a sterile procedure under continuous ultrasound guidance. Operators made every effort to avoid transplacental insertion. The first one ml of amniotic fluid was discarded and another 20 ml were aspirated for culture and chromosomal assessment. When bleeding occurred within the last two weeks prior to scheduled amniocentesis, the procedure was postponed for another two weeks. The result of chromosomal karyotyping was available at four weeks after the amniocentesis. Fetal sex would not be revealed in the result.

All clinical data was collected by an experienced medical secretary in the interview including maternal age, gestational age, positive obstetric history, abnormal vaginal bleeding in this pregnancy, amniotic fluid color, the number of insertion, fetal karyotype, and pregnancy outcome. Gestational age was calculated from the first day of the last menstrual period and confirmed or corrected by a first-trimester ultrasonography in all cases. Fluid samples were classified as clear, tinged, blood-tinged, and bloody. The data was updated if the patients had any complication after amniocentesis. After delivery, the relevant information about mother and neonate was collected via telephone.

Statistical analyses were all done with SPSS for Windows (version 13.0). Chi-square (x^2) test was used to analyse the difference of proportion. A $p < 0.05$ was defined significant.

Results

The women who had amniocentesis in the present hospital were 7,957. The median maternal age was 32.24 ± 5.53(18 - 49) years, the median gestational age was 20.79 ± 1.44 (18 - 26) weeks. Table 1 lists the indications for amniocentesis. The principal indication in the present study was increased risk of serum biochemical screening for Down syndrome (> 1/270) (46.21%) and advanced maternal age (> 35 years) (33.45%). Adequate amniotic fluid was obtained after one puncture in 7,818 (98.25%) procedures, two punctures in 123 cases (1.55%) and three punctures in 16 cases (0.2%). Transplacental insertion of the needle was required in 246 (3.09%) cases. Fluid was clear in 7,628 cases (95.86%), abnormally colored in 329 cases (4.14%), including tinged in 126 cases (1.58%), blood-tinged in 112 cases (1.41%) and bloody in 91 cases (1.14%).

Table 2. — *The abnormal karyotypes detected after amniocentesis.*

Nature of abnormality	n	%
Major chromosomal abnormalities	175	2.20
Trisomy 21	79	0.99
Trisomy 18	30	0.38
Other trisomies	22	0.28
45 XO	32	0.40
47 XXX	6	0.07
47 XXY	6	0.07
Minor chromosomal abnormalities	261	3.28
Balanced inversion	60	0.75
Balanced translocation	33	0.41
46 XY Y bigger or smaller than 22	13	0.16
Unbalanced Robertsonian translocations	18	0.23
Pseudomosaicism	137	1.72
Total	436	5.48

Table 3. — *The fetal loss after amniocentesis.*

Weeks after amniocentesis	Fetal loss	
	n	%
0-1	6	0.08
1-2	12	0.15
2-4	14	0.17
4-6	6	0.08
6-10	4	0.05
10+	5	0.06
Total	47	0.59

A total of 7,957 results of fetal karyotype were collected in the present study. There were 436 abnormal karyotypes (5.48%) in this study. The abnormal karyotypes included 175 major chromosomal abnormalities and 261 minor chromosomal abnormalities, judged to be of no clinical significance. The major chromosomal abnormalities included 79 cases of Trisomy 21, 30 Trisomy 18, 22 other trisomies, and 44 sex chromosomal abnormalities including 32 45 XO, 6 47 XXX, 6 47 XXY. Minor abnormalities included 60 balanced inversion, 33 balanced translocation, 13 46 XY Y bigger or smaller than 22,18 unbalanced Robertsonian translocations, and 137 pseudomosaicism (Table 2).

The number of complete follow-up information regarding pregnancy outcome was 7,921 collected in all 7,957 women. The loss follow-up rate was 0.45%. There were 256 (3.23%) elective termination of pregnancy and 68 (0.86%) unintended fetal loss. The total fetal loss rate after amniocentesis was 4.09 %. In 256 elective pregnancy termination cases, none was performed as a consequence of a complication due to amniocentesis. The unintended fetal loss rate after amniocentesis was 0.86%. All unintended fetal loss rate was considered as potentially procedure-related, except the eight neonatal deaths with major structural abnormalities, and the 13 cases with strong obstetric or non-obstetric causes. The cumulative fetal loss rates, including only these

47 potentially procedure-related cases (0.59%), were 0.08% within the first week of the amniocentesis, 0.23% within two weeks, 0.40% within four weeks, 0.48% within six weeks, and 0.53% within ten weeks (Table 3). The fetal loss rate up to 24 weeks and 28 weeks of gestation was 0.35% and 0.45% respectively.

The potentially procedure-related fetal loss rate was found to be significantly associated with maternal age (> 35 years) [0.84% (25 / 2988) vs 0.45% (22 / 4933), $p = 0.028$], previous fetal loss history [1.44% (10 / 696) vs 0.42% (37 / 7225), $p = 0.002$] and abnormal vaginal bleeding in this pregnancy [1.05% (15 / 1426) vs 0.49% (32 / 6495), $p = 0.00$]. However, the same difference was not detected in the number of punctures ($p = 0.78$), a transplacental insertion of needle ($p = 0.64$), or a discoloured amniotic fluid ($p = 0.32$).

Discussion

In the present study, the authors collected the data of 7,957 Chinese women who had an amniocentesis in the present hospital for any reason and pregnancy outcome of 7,921 women were also gathered. With the spread use of serum triple test screening for Down syndrome in clinic of China, the first indication of amniocentesis was the increased risk of serum biochemical screening for Down syndrome (> 1 / 270) instead of advanced maternal age, which was different from in western countries. In the present study, the median maternal age was 32.24 ± 5.53 years and 62.28% of the women were younger than 35 years. The authors took amniocentesis from 18 weeks to decrease the risk of fetal loss after amniocentesis [9], hence the median gestational age was 20.79 weeks. Of the women studied, 5.48% were found to have abnormal karyotypes. The proportion of women with major chromosomal abnormalities was 2.20%. The proportion of abnormal karyotypes was significantly higher in women with indication of abnormal karyotyping in either of couples (35.82%, 24 / 67) and positive sonographic markers for aneuploidies (13.12%, 45 / 343) than with other indications.

Follow-up information regarding the pregnancy outcome was gathered in 99.55% of 7,957 women in this study.The lost follow-up rate was only 0.45%. The total fetal loss rate was 4.09%, which included 3.23% elective pregnancy termination and 0.86% unintended fetal loss. In 68 unintended fetal losses, the authors found the accurate cause in eight neonatal deaths with major structural abnormalities and the 13 cases with strong obstetric or non-obstetric causes. Forty-seven unintended fetal loss cases were considered as potentially procedure-related. The fetal loss rate was 0.59% and 0.59% fetal loss rate after amniocentesis was not all actually attributable to the procedure, which also included some background fetal loss and some other reason for the loss. In general, to calculate the fetal loss rate attributable to the procedure, the background fetal loss and other reason loss rate must be subtracted; however the accurate background fetal loss rate cannot currently be gathered, because it requires a large randomized controlled trial. There was no control group, matched by age and previous obstetric history with the study group, in which an amniocentesis was not performed and such a trial could not be performed today because it would not be considered ethical, which could result in the failure to identify some cases with abnormal karyotype and thus the continuation of unwanted pregnancies. For these reasons the present authors could not give a precise fetal loss rate after amniocentesis only attributable to the procedure.

From the previous study, ultrasound-based studies have shown that the spontaneous fetal loss rate, assessed without considering maternal age and ethnicity, is approximately 1% after 16 weeks of gestation [10]. Seeds [7] analyzed first 15 studies with a total number of 6,457 controls without amniocentesis and second 14 studies with a total number of 12,097 controls without amniocentesis. The background fetal rate was 1.4% and 1.08%, respectively. From these background fetal loss rates, the present authors found that the fetal loss rate in this study was lower than those background fetal loss rates. Although initially surprising, the explanation is simple. Because these women with amnio- centesis had prenatal diagnosis, aneuploid pregnancies were identified and could thus be terminated. The higher background fetal loss rate in control group which did not undergo amniocentesis likely resulted from the spontaneous loss of undiagnosed aneuploid fetuses. It was impossible to gather the accurate background fetal loss rate after excluding the elective pregnancy termination and the accurate fetal loss rate after amniocentesis simply attributable to the procedure could not be gathered, but it was not important. Because the couples' decision depended on simply the outcomes: the risk of having a child with a chromosomal abnormality or a specific genetic disease compared with the risk of losing a normal pregnancy as a result of the procedure. From the present study, the authors discovered that 5.48% of all women with amniocentesis were found to have abnormal karyotypes and the proportion of women with major chromosomal abnormalities was 2.20%; on the contrary the fetal loss rate after elective pregnancy termination related to the procedure was lower than 0.59%. It was without a doubt that amniocentesis brought benefits for women who needed amniocentesis with the correct indication.

In the present study, unintended fetal loss rate after amniocentesis was lower than the other previous reports [11-15]. The reasons may include: (a) six operator was experienced and all the procedure was under continuous ultrasound guidance and the needle was 22-gauge; (b) because the increased risk of serum biochemical screening for Down syndrome (> 1/270) became the first indication instead of advanced maternal age, the median maternal age was younger in the present study. It is well known that fetal loss rate is higher in older women [16-18] as also proven by the present study outcome; (c) the median gestational age was 20.79 weeks in the present study which was later than

other reports. The fetal loss after amniocentesis was correlated with the gestational age [9, 12, 19]; (d) the elective pregnancy termination rate was 3.23%, which was higher than other reports. In the present study, virtually almost all Chinese women with a prenatal diagnosis of major chromosomal abnormalities and 20% of those with minor chromosomal abnormalities chose to terminate their affected pregnancies. This choice was different from reports from western societies [5, 20].

Conclusion

When an invasive amniocentesis is required, the couples will face a difficult choice: the risk of having a child with a chromosomal abnormality or a specific genetic disease compared with the risk of losing a normal pregnancy as a result of the procedure. The present study gave them the answer: 5.48% of all women with amniocentesis were found to have abnormal karyotypes and the proportion of women with major chromosomal abnormalities was even 2.20%; on the contrary the fetal loss rate related to the procedure was lower than 0.59%. Therefore amniocentesis should be recommended to all women who require it.

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