Pregnancy Loss Rates After Midtrimester Amniocentesis

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OBJECTIVE: The purpose of this study was to quantify the contemporary procedure-related loss rate after midtrimester amniocentesis using a database generated from patients who were recruited to the First And Second Trimester Evaluation of Risk for Aneuploidy trial.

METHODS: A total of 35,003 unselected patients from the general population with viable singleton pregnancies were enrolled in the First And Second Trimester Evaluation of Risk for Aneuploidy trial between 10 3/7 and 13 6/7 weeks gestation and followed up prospectively for complete pregnancy outcome information. Patients who either did (study group, n=3,096) or did not (control group, n=31,907) undergo midtrimester amniocentesis were identified from the database. The rate of fetal loss less than 24 weeks of gestation was compared between the two groups, and multiple logistic regression analysis was used to adjust for potential confounders.

RESULTS: The spontaneous fetal loss rate less than 24 weeks of gestation in the study group was 1.0% and was not statistically different from the background 0.94% rate seen in the control group (P=.74, 95% confidence interval −0.26%, 0.49%). The procedure-related loss rate after amniocentesis was 0.06% (1.0% minus the background rate of 0.94%). Women undergoing amniocentesis were 1.1 times more likely to have a spontaneous loss (95% confidence interval 0.7–1.5).

CONCLUSION: The procedure-related fetal loss rate after midtrimester amniocentesis performed on patients in a contemporary prospective clinical trial was 0.06%. There was no significant difference in loss rates between those undergoing amniocentesis and those not undergoing amniocentesis.

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LEVEL OF EVIDENCE: II-2

The first amniocentesis performed for genetic indications (sex determination) was reported by Fuchs and Riis[1] in 1956. Ten years later, Steele and Breg[2] demonstrated that the cells in the amniotic fluid could be cultured to yield a fetal karyotype. Currently, amniocentesis is the most common invasive test used to prenatally diagnose chromosomal and genetic abnormalities. In 2003, almost 70,000 amniocentesis procedures were performed in the United States alone.[3]

The pregnancy loss rate after midtrimester amniocentesis is usually quoted to be approximately 0.5%. This traditionally quoted risk is based on a recommendation from the Centers for Disease Con-

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trol and Prevention.[4] It was derived from three nationally sponsored studies in the United States, Canada, and Great Britain performed in the 1970s.[5,6,7] These studies were not randomized and were performed in an era when continuous ultrasound guidance for amniocentesis was not routine. Additionally, even though ultrasonography was available, the clarity of ultrasound in the 1970s was far inferior to what it is today. Based on anecdotal experience and the issues mentioned above, many clinicians feel that the traditionally quoted risk of 0.5% for amniocentesis is an overestimate.

Nonetheless, the only large-scale prospective randomized study evaluating pregnancy loss rates after midtrimester amniocentesis was published by Tabor et al[8] in 1986. This study showed a 1% greater pregnancy loss rate in patients randomly assigned to undergo amniocentesis compared with those assigned to undergo ultrasound surveillance alone. Concerns raised about this study include the unexpectedly low background loss rate in the nonamniocentesis group. The Canadian Early and Mid-Trimester Amniocentesis Trial was a randomized study to compare amniocentesis at less than 13 weeks of gestation to amniocentesis at 15 weeks or more.[9] Although there was not a "no procedure" group in that study, the unintended loss rate less than 20 weeks in the 15-week-or-more amniocentesis group was 0.96%. A recent contemporary evaluation of amniocentesis loss rates was recently undertaken by Seeds.[10] In his review of 29 controlled studies evaluating losses after amniocentesis, he concluded that when performed with concurrent ultrasound guidance, the procedure-related loss rate was 0.6%

Based on the conflicting results in the studies mentioned above, the true procedure-related loss rate after amniocentesis remains controversial. The purpose of this study was to estimate the contemporary procedure-related loss rate after midtrimester amniocentesis using a large database generated from unselected patients who entered a multicenter prospective clinical trial (the First And Second Trimester Evaluation of Risk; FASTER trial).

MATERIALS AND METHODS

The FASTER trial was an National Institute of Child Health and Human Development–sponsored multicenter trial designed to compare first-trimester Down syndrome screening with nuchal translucency, pregnancy-associated plasma protein A, and free β-hCG to second-trimester screening with alpha-fetoprotein, hCG, unconjugated estradiol, and inhibin-A.[11] The FASTER consortium consisted of 15 clinical centers distributed throughout the United States (see Appendix). Briefly, unselected patients from the general population with viable singleton pregnancies were enrolled in the FASTER trial between 10 3/7 and 13 6/7 weeks of gestation and followed up prospectively for complete pregnancy outcome information. The study enrollment period was 1999–2002. Patients who were screen positive in either the first (defined as a Down syndrome risk of 1:150 or more) or second (defined as a Down syndrome risk of 1:300 or more) trimesters underwent genetic counseling by a specially trained counselor and were offered amniocentesis. Some patients who were screen negative in both trimesters elected to undergo amniocentesis. All amniocentesis procedures were performed according to each center's local clinical practice, by either perinatologists or general obstetrician–gynecologists. No data were collected concerning the experience of the person doing the amniocentesis or the size of the needle used for the procedure. Pregnancies were followed to term and all infants were examined at birth for features of Down syndrome or other abnormalities. Patients who declined amniocentesis prenatally were offered karyotyping of their neonates. Maternal demographics, medical history, obstetric history, and information about the outcome of the current pregnancy were stored in a secured database. Participation in the FASTER trial was approved by the institutional review board at each of the participating centers.

Women who enrolled in the trial but terminated their pregnancies before the time for amniocentesis (n=171) or whose outcome information was unknown (n=1,770) were excluded from the analysis. There were no significant differences between patients with outcome information and those without outcome information with respect to age, parity, body mass index (BMI), prior preterm birth or prior miscarriage. After the exclusions mentioned above, 35,003 patients were available for inclusion in our analysis. The crude rates of spontaneous pregnancy loss <24 weeks were compared between the amniocentesis and no amniocentesis groups using Fisher exact test and 95% confidence intervals (CI) were calculated. Spontaneous loss was defined as any unintentional pregnancy loss <24 weeks. Below 24 weeks was chosen to define pregnancy loss, because this is currently considered by most clinicians to be the threshold of viability. Older studies evaluating amniocentesis included losses up to 28 weeks, but these studies were performed at a time when the threshold of viability was later in gestation than generally considered today. The crude loss rates <24 weeks between the amniocentesis and no amniocentesis groups stratified by FASTER screen results and maternal age were compared in a similar fashion.

To account for potential confounders, adjusted odds ratios were generated using multiple logistic regression analysis. Only covariates that were statistically significant in bivariate analysis were considered for inclusion in the final multivariable model. Potential confounders included maternal age, BMI, parity, prior adverse pregnancy outcome (miscarriage at less than 20 weeks of gestation, induced abortion or termination at less than 24 weeks of gestation, preterm delivery at less than 37 weeks of gestation, prior fetus or child with a chromosomal abnormality, prior fetus or child with a genetic disorder), FASTER screen status (screen positive on either first or second, or screen negative on both), threatened abortion in the current pregnancy (vaginal spotting/bleeding), maternal diabetes status and maternal use of alcohol or medications (antihypertensives, anticoagulants, thyroid medications) after becoming pregnant. The significant covariates included in the final model were maternal age, BMI, history of diabetes, parity, previous preterm delivery, previous miscarriage, previous termination, previous chromosomal abnormality, previous genetic disorder, threatened abortion, medication use, alcohol use, and FASTER screen status. Adjusted odds ratios, *P* values and 95% confidence intervals were calculated. We examined differences in loss rates for women undergoing amniocentesis compared with those not undergoing amniocentesis across the different enrollment centers using the Breslow Day test for homogeneity of effect. The associations were not significantly different among centers, thus data from centers were pooled for analysis.

RESULTS

The FASTER trial database for this analysis contained information on 35,003 pregnancies and their outcomes. There were 331 patients in the overall group who had spontaneous pregnancy losses at less than 24 weeks of pregnancy (0.95%), and within this group, 31 patient's losses were subsequent to midtrimester amniocentesis. The amniocentesis group consisted of 3,096 patients identified from the database who underwent midtrimester amniocentesis (8.8% of total). The control group consisted of 31,907 patients (91.2% of total) who did not undergo amniocentesis. Table 1 shows the total proportion of pregnancy losses in all patients and in the subgroups of patients who elected either to undergo or not undergo amniocentesis. The overall spontaneous loss rate in the amniocentesis group was 1.0% and 0.94% in the no amniocentesis group. The difference between these two groups was not significant ($P=.74$). Assuming that the 0.94% rate of pregnancy loss in the control group (no amniocentesis) is the "background" loss rate, the loss rate attributable to amniocentesis is 0.06% (1.0% minus 0.94%). This is a nonsignificant difference with a 95% confidence interval (CI) of −0.26% to 0.49%. In the group not undergoing amniocentesis, 67 patients (0.2%) electively terminated their pregnancies, compared with 91 patients (2.9%) in the amniocentesis group ($P<.0001$). Information about the reasons for these elective terminations was not available.

In the subgroup of women who were FASTER screen positive in either the first or second trimester (n=3,446, 9.8% of the total), the rate of spontaneous loss was 1.06% in those undergoing amniocentesis

Table 1. Observed (Crude) Spontaneous Loss Rates (with 95% Confidence Interval) for All Cases, Cases With Amniocentesis Performed, Cases With Amniocentesis Not Performed, and the Difference Between the Two Latter Groups Under a Variety of Conditions

Condition	Spontaneous Loss Rates for All Cases (n=35,003)	Spontaneous Loss Rates With Amniocentesis Performed (n=3,096)	Spontaneous Loss Rates With Amniocentesis Not Performed (n=31,907)	Difference in Spontaneous Loss Rates With Amniocentesis Performed and Not Performed
All cases (N=35,003)	0.95 (0.85–1.05)	1.00 (0.68–1.42)	0.94 (0.84–1.05)	0.06 (−0.26–0.49)
Screen positives only* (n=3,446)	2.44 (1.95–3.01)	1.06 (0.63–1.68)	3.76 (2.92–4.76)	−2.70 (−3.78 to −1.71)
Screen negatives only* (n=31,557)	0.78 (0.69–0.89)	0.93 (0.49–1.58)	0.78 (0.68–0.88)	0.15 (−0.25–0.81)
Maternal age 35 y or older (n=7,085)	1.68 (1.39–2.01)	1.06 (0.66–1.62)	1.92 (1.56–2.33)	−0.86 (−1.41 to −0.21)
Maternal age younger than 35 (n=27,918)	0.76 (0.66–0.87)	0.89 (0.43–1.63)	0.75 (0.65–0.86)	0.14 (−0.29–0.88)

Data are loss rate (95% confidence interval).
*First and Second Trimester Evaluation of Risk screen positive/negative in either first or second trimester.

compared with 3.76% in those not undergoing amniocentesis. This difference of 2.7% was statistically significant (95% CI 3.78–1.71%). In the patients who were FASTER screen negative, the rate of spontaneous loss was lower (0.78%) in the no amniocentesis group than in the amniocentesis group (0.93%); however, this difference was not statistically significant (0.15, 95% CI −0.25%, 0.81%).

Women who were aged 35 years or older and elected to undergo amniocentesis had a spontaneous pregnancy loss rate of 1.06%. Those electing not to undergo amniocentesis had a spontaneous loss rate of 1.92%. The 0.86% higher loss rate in the no amniocentesis group was statistically significant (95% CI 0.21–1.41). Amniocentesis compared with no amniocentesis losses in women aged younger than 35 years were 0.89% and 0.75%, respectively. This difference of 0.14% (95% CI −0.29%, 0.88%) was not statistically significant.

Table 2 shows the potential confounders evaluated for the multivariable analysis. Table 3 shows crude and adjusted odds ratios in a model adjusting for the potential confounders that were significant at the bivariate level. In the overall group, the patients who were screen negative and women aged younger than 35 years, the crude odds ratios, as expected, were all approximately 1 (1.1, 1.2, and 1.2, respectively). The adjusted odds for loss in the overall group, in the patients who were screen positive and in the patients who were aged 35 years or older were 0.4, 0.3, and 0.4, respectively. These were all statistically significant. The adjusted odds ratio for patients who were screen negative was 1.0, which was not significant. In women aged younger than 35 years, the adjusted odds ratio was 0.5. This approached but did not reach statistical significance (P=.07).

Table 4 shows a breakdown of the spontaneous pregnancy losses less than 24 weeks of pregnancy

Table 2. Comparison of Potential Confounders Between the Cases With Amniocentesis Performed Compared With the Cases Without Amniocentesis Performed

Characteristic	Amniocentesis Performed (n=3,096)	Amniocentesis Not Performed (n=31,907)	*P*
Maternal age	35.7 (±4.76)	29.4 (±5.52)	<.001
Maternal AMA (35 y or older)	63.7	16.0	<.001
Body mass index			<.001
30–35	7.2	9.5	
35 or more	4.9	5.6	
Diabetes	1.4	1.0	.028
Previous pregnancy	75.9	67.7	<.001
Previous preterm pregnancy	7.2	6.7	.231
Previous miscarriage	33.8	25.5	<.001
Previous termination	29.0	16.1	<.001
Previous chromosomal abnormality	4.0	1.0	<.001
Previous genetic disorder	0.5	0.2	.004
Family history of genetic disorder*	0.8	0.7	.563
Down screening result	54.6	5.5	<.001
Threatened abortion			.001
Vaginal spotting	14.9	12.5	
Vaginal bleeding	1.6	1.7	
Smoker*	4.3	4.7	.255
Drinker	4.1	1.9	<.001
Antibiotics use*	13.2	13.7	.491
Marijuana use*	0.5	1.0	.007
Cocaine use*	0.03	0.1	.254
Heroin use*	0.0	0.05	.390
Antihypertensives use	1.4	0.6	<.001
Cardiac medications use*	0.2	0.1	.375
Anticoagulants use	2.1	1.1	<.001
Antiepileptics use*	0.5	0.4	.322
Thyroid replacements use	5.8	3.4	<.001
Antithyroids use*	0.4	0.1	.007
Antidepressants use*	3.9	3.6	.496
Steroids use*	1.5	0.7	<.001

AMA, advanced maternal age.
Data are mean (±standard deviation) or %.
* Not used as a covariate in regression modeling due to lack of effect at the univariable level.

Table 3. Crude and Adjusted Odds Ratios and *P* Values for the Relationship Between Amniocentesis and Spontaneous Loss Under a Variety of Conditions

Condition	Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)*	Adjusted *P*
All cases (N=35,003)	1.1 (0.7–1.5)	.74	0.4 (0.3–0.7)	<.01
Screen positives only (n=3,446)	0.3 (0.2–0.5)	<.01	0.3 (0.2–0.4)	<.01
Screen negatives only (n=31,557)	1.2 (0.7–2.1)	.54	1.0 (0.6–1.8)	.89
Maternal age 35 y or older (n=7,085)	0.6 (0.3–0.9)	.01	0.4 (0.2–0.6)	<.01
Maternal age younger than 35 y (n=27,918)	1.2 (0.6–2.2)	.61	0.5 (0.3–1.1)	.07

OR, odds ratio; CI, confidence interval.

* Model adjusted for maternal age, body mass index, diabetes, previous pregnancy, previous fetus with problems (ie, miscarriage, abortion, preterm delivery, chromosomally abnormal, genetic disorder), Down screen status (positive or negative), threatened abortion, and maternal use of alcohol or medications (only significant covariates kept in the model based on a combination of univariate analysis and use of backward logistic regression).

Table 4. Time Until Loss After Amniocentesis (n=21)

Time Until Loss After Amniocentesis (wk)	n (% of cases)
Less than 2	13 (61.9)
2–4	6 (28.6)
4–8	1 (4.8)
More than 8	1 (4.8)

There were 31 cases used for analysis that had an amniocentesis and a spontaneous loss; however, 10 cases were missing either the date of amniocentesis or the date of loss and so are not included here.

with respect to the length of time after the amniocentesis when the losses occurred. Ten patients with postamniocentesis losses are not included in this table because data concerning the timing of the loss after the amniocentesis was lacking. The median time to pregnancy loss was 3 days in the patients for whom these data are available.

DISCUSSION

A further randomized trial of amniocentesis compared with no amniocentesis to try to define contemporary procedure-related loss rates is not likely to be performed due to feasibility and ethical considerations. The best surrogate to evaluate the safety of this procedure, therefore, is to examine the largest number of patients possible in a nonrandomized sample drawn from an unselected population in a prospective multicenter trial, which has been made possible by the design of the FASTER trial. The positive aspects of our study include the large number of patients, the multicenter design reflecting practices across the United States, the completeness of pregnancy outcome data, a fixed clinical protocol, a relatively short time frame for the study and its contemporary study period. Potential limitations of our study include its nonrandomized design, limited information concerning the experience of the clinicians performing the procedures, the needle size used for the procedure, and potential underpowering of the study to detect subtle differences in stratified analysis. With respect to operator experience and needle size, the strength of our data lies in the fact that it reflects contemporary practice in the community and not some idealized way of performing the procedure in expert hands. In other words, our results are more likely to be generalizable to the community than a protocol that required the procedures to be performed by select experts using specified techniques. With respect to sample size, more than 400,000 women would be needed in each arm to have 80% power to detect a difference of 0.05% in spontaneous loss rates between those who did and did not undergo amniocentesis. Despite the limitations mentioned above, this study provides the best possible contemporary information about procedure-related loss rates after amniocentesis and calls into question the relevance of commonly quoted higher loss rates from older studies.

In the crude model, the difference between losses in the amniocentesis compared with no amniocentesis groups was not significant. The 1.0% unintended pregnancy loss rate in the amniocentesis group of our study is similar to 0.96% rate of loss seen in the midtrimester amniocentesis group of the Canadian Early and Mid-Trimester Amniocentesis Trial study.[9] In the adjusted model, the odds of pregnancy loss were actually *lower* in patients who underwent amniocentesis compared with those who did not. This is likely due to the fact that spontaneous pregnancy loss is so strongly associated with aneuploidy, and patients who have an amniocentesis would presumably terminate aneuploid fetuses in most cases before a spontaneous loss could occur. This presumption is substantiated by the subgroup analysis for screening status and maternal age. Patients who were screen positive or aged 35 years or older were at the highest risk of having chromosomally abnormal pregnancies, which

are known to have a higher rate of spontaneous loss. Patients in these categories who underwent amniocentesis were more likely to terminate chromosomally abnormal pregnancies after they had been detected (thus obviating the possibility of a spontaneous loss). It is not surprising, therefore, that patients in these categories who elected *not* to undergo amniocentesis, had a higher rate of spontaneous loss because they were carrying a higher proportion of aneuploid fetuses. This was reflected in both the crude and adjusted odds ratios.

We were unable to explicitly use aneuploidy in the regression modeling because information about aneuploidy was missing from some of the spontaneous losses. This is not surprising given that many patients with spontaneous pregnancy loss before 20 weeks of gestation may do so outside of the hospital setting and without availability of subsequent karyotypic analysis. Screen-negative patients, however, are a useful surrogate for euploid pregnancies and *were* included in the model. The crude and adjusted odds ratios for that group were both approximately 1. This finding suggests that if one minimizes or eliminates the effect of aneuploidy, then amniocentesis itself has an extremely low risk of causing pregnancy loss. For women aged younger than 35 years, the crude odds for pregnancy loss, as expected, was near 1, and the difference between those undergoing amniocentesis and not undergoing amniocentesis was not statistically significant.

For 10 of the 31 spontaneous losses after amniocentesis, no information is available with respect to the timing of the pregnancy loss. This is one of the limits of a population-based cohort study. In particular, patients who had such an outcome would have been predictably upset and even less likely to be responsive to follow-up calls from data collectors than patients who did not have a pregnancy loss. This is a scientific reality of data collection on a sensitive topic.

The observed difference in crude pregnancy loss rates less than 24 weeks between the amniocentesis and no amniocentesis groups was 0.06%. This equates to an amniocentesis procedure-related loss risk of approximately 1 in 1,600 and is substantially lower than the traditionally quoted risk of 1 in 200. Such contemporary data will likely have a significant effect on how patients are counseled in current clinical practice and may also have a significant effect on choices regarding invasive and noninvasive screening for fetal aneuploidy. Based on the primary outcomes of the FASTER Trial and the information in this study, the practice of routinely offering amniocentesis to women after age 35 years has become arbitrary and archaic. This should be abandoned for a more customized risk assessment using information specific to the pregnancy being evaluated, rather than maternal age alone.

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APPENDIX

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