

Mid-Trimester Amniocentesis Fetal Loss Rate

This committee opinion has been approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To determine the postprocedure loss rate for mid-trimester genetic amniocentesis.

Outcome: Reduction of benign biopsy rates.

Benefits: To provide better advice for women about the risks and benefits of mid-trimester genetic amniocentesis, and to ensure that women are given sufficient information/counselling to make a decision about screening.

Summary Statement: The risk of postprocedure loss is unique to the individual and is based on multiple variables.

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MID-TRIMESTER AMNIOCENTESIS: WHAT IS THE REAL POSTPROCEDURE LOSS RATE?

Genetic mid-trimester amniocentesis is the most commonly used invasive procedure for prenatal diagnosis of chromosomal and single gene disorders. Traditionally, the procedure has been offered to women aged 35 years or over and those at increased risk of a chromosome abnormality on the basis of personal/family history or non-invasive prenatal screening (ultrasound and/or biochemical) test results. The recommended maternal age for the procedure was selected because the risk of a 35-year-old mother to have a child with a chromosomal abnormality was approximately equal to the risk of miscarriage due to the procedure, which in most Canadian centres is quoted to be 0.5% (1/200).¹ This approach is now obsolete in the context of enhanced non-invasive screening modalities and the recently published SOGC guideline,² which recommends that it is no longer appropriate to offer women amniocentesis on the basis of maternal age alone; rather, all pregnant women should be offered multiple marker screening, and only those with screening test results above a pre-determined cut-off should be offered invasive testing. Maternal age of 40 or over at delivery is considered to carry a high enough prior risk to warrant offering the option of screening or of proceeding directly to invasive diagnosis.

Key Words: Pregnancy, genetic amniocentesis, prenatal screening, miscarriage

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BACKGROUND

Two types of loss reported in the literature should be considered: (1) total pregnancy loss rate postprocedure, which includes both background pregnancy loss for that gestational age and procedure-related loss, and (2) procedure-related pregnancy loss. The total post-amniocentesis loss rates are derived from studies of populations of pregnant women who underwent amniocentesis, with a control group consisting of populations of pregnant women who had another procedure or no control group. The amniocentesis-related pregnancy loss rates are derived from studies of pregnant women who had amniocentesis compared with a “no procedure” control group.

A recently published study by Eddleman et al.³ suggests that the procedural loss rate of amniocentesis may be much smaller than previously reported, further challenging the indications for invasive testing in the context of a traditional “risk-benefit” ratio. Although the committee agrees that it is timely to re-evaluate this issue, we believe Eddleman’s conclusion that the rate of miscarriage due to amniocentesis is 0.06% (1/1600) is misleading and should be interpreted with caution.³ The study is based on a secondary analysis of data from the “First and Second Trimester Evaluation of Risk for Aneuploidy” (FASTER) trial,⁴ the primary goal of which was to compare first and second trimester noninvasive prenatal genetic screening methods. Among the 35 003 women enrolled, 3096 women underwent amniocentesis (the study group) and 31 907 women (the control group) did not have an amniocentesis. The rate of spontaneous fetal loss prior to 24 weeks gestation in the study group was 1%, not statistically different from the control group rate of 0.94%. The risk of miscarriage due to amniocentesis was reported to be no different between these two rates, which was 0.06% (1/1600). However, the rates in the study group did not include pregnancies terminated for a chromosomal abnormality, whereas in the control group (no amniocentesis) pregnancies spontaneously lost, including chromosomally abnormal pregnancies, were counted. Presumably, many of the pregnancies terminated in the study group were destined to be lost spontaneously, and their exclusion underestimates the rate of pregnancy loss in the study group compared with the control group. Furthermore, it is important to recognize that patients in these prospective groups were highly selected and may not be comparable to most patients undergoing amniocentesis.

Letters to the editor have criticized the FASTER conclusion.⁵⁻⁹ Nadel⁵ commented that although the difference in the unadjusted risk of fetal loss at less than 24 weeks between the amniocentesis and no amniocentesis groups was not statistically significant ($P = 0.74$), the difference in the point estimates between these two groups (0.06%) had a

95% confidence interval (CI) of -0.26% to 0.49%. He concluded that the likelihood of amniocentesis resulting in the loss of a euploid fetus is less than 0.5% (but it is not known exactly how much less).

Smith⁷ commented that the methods used to include or exclude pregnancy termination patients resulted in the paradox of a statistically significant increase in spontaneous abortion for women not having amniocentesis with a positive screen and women who were aged 35 years or over. The lowest rate of risk for genetic amniocentesis derived from the literature is about 1 in 300.⁸

COUNSELLING

In counselling patients prior to amniocentesis, it is important to convey to patients that at their stage of pregnancy there is a background pregnancy loss rate, and that amniocentesis will contribute an additional procedure-related loss rate. The notion of background population or individual background rate is important, as the patient will not be able to determine whether her pregnancy loss was “background” or “procedural.” Counselling should provide a patient with the total pregnancy loss rate to enable her to understand the possible sequelae of her decision. Individual procedural risks may be required for counselling because of the real variables that contribute to the population or individual background risk.

A. Patient Factors

1. Maternal age/ paternal age¹⁰⁻¹⁴
2. Past reproductive history¹³
3. Pre-existing maternal conditions (diabetes, hypertension, infertility, autoimmune)
4. Pregnancy/uterine (assisted reproductive techniques, vaginal bleeding, uterine fibroids, placental location, amniotic fluid loss, oligohydramnios, retro chorionic hematoma, single vs. multiple gestations)¹⁶⁻¹⁹
5. Screening methodology²⁰
 - i) timing (first trimester, second trimester, first and second trimester)
 - ii) technique (ultrasound alone, biochemistry, biochemistry and ultrasound, nuchal translucency +/- biochemistry, single or multiple soft markers or congenital anomalies)

Summary of studies with mid-trimester amniocentesis populations

A. Total pregnancy loss rates post amniocentesis

Study	Type	Mid-trimester amniocentesis	Control	Post-amniocentesis loss rate	Significance
Smidt-Jensen (1992) ²⁶	RCT	1042	CVS TC 1010 TA 1027	1.16%	—
Lippman (1992) ²⁷	RCT	1200	CVS 1191	0.9% (0.3% < 4 weeks)	—
Johnson (1996) ²⁸	RCT	339	EA 344	3.3%	NS
CEMAT (1998) ²⁹	RCT	1775	EA 1916	1.0%	—
Collins (1998) ³⁰	C	1747	EA1207	1.1%	—
Reid (1999) ³¹	C	3953	—	0.7%	—
Antsaklis (2000) ³²	C	3910	other amnio* 5324	2.1% / 1.5%	P = 0.01
Horger (2001) ³³	C	4600	—	0.7%	—
Caughey (2006) ³⁴	C	30 893	CVS 9886	0.5% (crude), 0.46% (adjusted)	—

B. Procedure-related pregnancy loss rate

Study	Type	Mid-trimester amniocentesis	Control (no procedure)	Procedure-related loss rate (no procedure group; loss rate no procedure group)	Significance
Tabor (1986) ³⁵	RCT	2302	2304	0.7% (3.2%; 2.2%)	NS
Muller (2002) ³⁶	C	3472	4191	0.7% (1.12%; 0.42%)	95% CI 0.39—1.13
Kong (2006) ³⁷	C	3468	1125	0.86% (corrected for background loss rate)	95% CI 0.19—1.53
FASTER (2006) ³	C	1096	31 907	0.06% (1.0%; 0.94%)	95% CI -0.26—0.49
Seeds (2004) ³⁸	Review	11 372	10 097	0.6% (1.68%; 1.08%)	95% CI 0.31—0.9

RCT: Randomized controlled trial; C: cohort study; CVS: chorionic villus sampling (TA: transabdominal; TC: transcervical); EA: early amniocentesis; RR: relative risk; CI: confidence interval; NS: not significant difference.

* Study group: women 20–34 years of age having amniocentesis for increased risk of aneuploidy or maternal infection; control group: women 20–34 years of age at low risk but having amniocentesis.

B. Procedure Factors

1. Amniocentesis needle size variation²¹
2. Operator experience^{22–24}
3. Ultrasound guided (freehand; needle guide)
4. Uterine/placental location
5. Maternal BMI

C. Postprocedure Factors

1. Rest for 24 hours or normal activity (no evidence-based comparisons available)
2. Complications (ruptured membranes, infection)²⁵

The Table summarizes the recent published reports (randomized controlled trials and cohort studies with or without a control group; the control group may have no

procedure or an alternative procedure), showing a range of post mid-trimester amniocentesis losses of 0.75 to 3.3% (9 studies; mean 1.41%, median 1.1%). Four studies compared mid-trimester amniocentesis with no procedure and showed a range of differences, with higher losses after amniocentesis of 0.06% to 1.0% (mean 0.64%; individual study loss rates 1.0%, 0.80%, 0.70%, 0.06%). On the basis of the confidence intervals for the procedure-related increased loss rate in this second group of controlled studies (minus FASTER results), the range is from 0.19% to 1.53%.^{26–38} Seeds, in a statistical analysis of amniocentesis risks from published studies, reported that the procedure-related pregnancy loss rate is 0.6% on the basis of the difference between the pregnancy loss rates in the control (1.08%) and procedure (1.68%) groups (CI 0.31–0.9).³⁸

The FASTER study pregnancy loss difference (amniocentesis; no amniocentesis) is a clear outlier within these controlled study groups and reflects that this study's method of analysis underestimated the procedure-related pregnancy loss rate following mid-trimester amniocentesis by excluding the terminated pregnancies in the amniocentesis group, resulting in a lower intrinsic rate of pregnancy loss for this group than for the control group.^{3,4}

SUMMARY

There is *no* single percentage (or odds ratio) that can be quoted as the risk of pregnancy loss following mid-trimester amniocentesis in singleton pregnancies. The risk is unique to the individual and is based on multiple variables, as summarized in this opinion. The best estimate range to consider for the increased rate of pregnancy loss attributable to amniocentesis is 0.6% to 1.0% (1/175–1/100) but may be as low as 0.19% or as high as 1.53% on the basis of the confidence intervals (CI) seen in the various studies. The best risk estimate for twin pregnancies was recently published and is 1.6% (CI 0.3–3%).¹⁶

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