Amniocentesis: Safety, Reliability and Alternatives

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Amniocentesis is the most commonly used technique for prenatal genetic diagnosis. It is an effective procedure with a high diagnostic success rate, but carries the risk of severe complications including miscarriage. Despite the risks, amniocentesis performed in the second trimester remains the safest means of prenatal genetic diagnosis. With the introduction of biochemical and first trimester ultrasound screening for fetal aneuploidy, amniocentesis usage rates have declined.

Background of Prenatal Genetic Screening

Pregnancy can be a time of worry, when concerns over fetal health and well-being are at the forefront of many women's minds. Modern clinicians have a wide array of tools at their disposal to allay parents' fears. Prenatal screening for genetic anomalies has become a cornerstone of care for expectant mothers.

In Ontario, Integrated Prenatal Screening (IPS), Serum Integrated Prenatal Screening (SIPS), and First Trimester Screen (FTS) are offered to all women presenting before 14 weeks gestation.¹ The testing uses serum markers and nuchal translucency (in the case of IPS and FTS) to assess the risk of trisomies 18 and 21 along with open neural tube defects. Testing is undertaken in both the first and second trimester, with results becoming available after the second set of testing. Many screening options are possible but IPS and SIPS (if nuchal translucency is not available) prove most accurate and safe.²³ These tests give the mother the risk of her fetus having one of these conditions, but are not diagnostic.

The costs to the health care system of screening have been estimated to be around $15,000 US per quality adjusted life year gained.⁴ The screening tests are non-invasive and do not pose a risk to the fetus in and of themselves, but are associated with an increased risk of pregnancy loss due to follow-up diagnostic tests. After a woman has screened positive as having increased risk of one of the fetal anomalies, she must be offered further testing; screening should therefore only be performed when follow-up diagnostic testing is available. When used in the absence of screening, based on maternal age, amniocentesis and chorionic villus sampling cost about $100,000 US per abnormal birth averted, giving substantial weight to the use of screening programs as a first step in assessing the risk of genetic abnormalities in a fetus.⁵ From a safety perspective, however, the use of amniocentesis with the sole risk factor of advanced maternal age is justified as the risk of aneuploidy is comparable to the risk of miscarriage.⁶

Positive Screen: What Comes Next?

Several options are available after a woman has screened positive: she can choose to continue the pregnancy without further testing, she can have chorionic villus sampling (CVS) in the case of FTS, or she can have amniocentesis. Both CVS and amniocentesis are invasive procedures that pose risks to the fetus, but are also highly effective diagnostic tools with close to 100% diagnostic success rates.⁷⁸

Amniocentesis involves the withdrawal of amniotic fluid from the uterine cavity. Typically, a 20 or 22 gauge needle is inserted into the amniotic sac transabdominally under ultrasound
guidance. It can be done both for obtaining cells to culture for genetic testing, fetal blood typing, and diagnosing fetal infection. When used for genetic diagnosis, amniocentesis is typically performed in the second trimester. It is most effective at obtaining a useful sample after 15 weeks gestation and before 24 weeks. Cell cultures typically take 7 days to grow before they can be tested. For more rapid results, interphase fluorescence in situ hybridization (FISH) can detect aneuploidy of chromosomes 13, 18, 21, X, Y in one to two days. An alternate procedure for obtaining genetic material from the fetus is chorionic villus sampling (CVS). CVS involves sampling the placenta either transabdominally or transcervically. It is usually performed in the first trimester, after 10 weeks gestation. The rate of both amniocentesis and CVS use has decreased with the introduction of IPS, FTS, and SIPS.

Safety of Early Versus Late Amniocentesis and CVS

The safety of early versus late (first rather than second trimester) amniocentesis and CVS has been studied extensively in the literature. Earlier testing provides a definitive diagnosis much quicker after a positive test, but is not without added risk of complication. A Cochrane review of 16 randomized controlled trials found second trimester amniocentesis to be the safest method of prenatal genetic diagnosis. Amniocentesis performed before the second trimester is associated with a higher rate of pregnancy loss (7.6% versus 5.9% relative risk of 1.29 95% CI 1.09 to 1.81) than second trimester testing, thus it is not as safe an alternative as later amniocentesis. CVS is the safest method of first trimester sampling, but has a higher loss rate than second trimester amniocentesis with a higher total pregnancy loss (relative risk of 1.40; 95% CI 1.09 to 1.81) and spontaneous miscarriage (9.4%; RR 1.50; 95% CI 1.07 to 2.11).

Risks of Amniocentesis

The maternal risks of amniocentesis are low; of much greater concern are potential fetal complications. The only randomized controlled trial comparing second trimester amniocentesis to placebo, a study of 4606 low risk women aged 25-34 years, found the rate of spontaneous abortion to be 1.7% in the second trimester amniocentesis group versus 0.7% in the control ultrasound group (relative risk of 2.3). Current consensus from various trials estimates the loss rate from second trimester amniocentesis to be between 0.6% to 1.0%. Fluid leakage is more common after amniocentesis than in controls, but is not associated with negative pregnancy outcomes.

With ultrasound guidance, direct fetal injury is extremely rare, although it has been reported. Indirect fetal injury is more common, with respiratory distress syndrome and pneumonia being more common in newborns after second trimester amniocentesis. A large cohort study of women 35-49 years old (with 71,586 participants) found an increased incidence of musculoskeletal deformities and respiratory distress in newborns whose mothers underwent 2nd trimester amniocentesis. There was no increase in limb reduction defects, infant and fetal mortality, prematurity, low birth weight, or fetal distress with amniocentesis. There is no long term increased risk for disabilities in children after amniocentesis.

Vertical transmission of infections such as cytomegalovirus, hepatitis C Virus, and human immuno deficiency virus has been linked to amniocentesis performed in infected women. Like all invasive procedures in chronically infected women, amniocentesis should be used only when absolutely necessary.

Advantages of Early Versus Late Diagnosis

Although second trimester amniocentesis has been conclusively shown to be the safest method of prenatal genetic diagnosis, it is not without disadvantages. Because it is performed in the second trimester, there is a long lag time between a screen positive test from IPS or SIPS and definitive diagnosis. CVS is available in the first trimester, thus cutting the lag time considerably. Several studies of women's subjective well being have shown shorter time to maternal fetal bonding, earlier anxiety reduction,
and improved health related quality of life in women having a positive screening test followed by a negative CVS as compared to a negative second trimester amniocentesis. The magnitude of the reduction of anxiety post test is the same for the CVS and amniocentesis groups, but occurs sooner because the CVS is done earlier. This benefit in anxiety reduction exists despite the increased risk for miscarriage with CVS. The same is true for the maternal-fetal bonding improvements, the bonding improves markedly after a negative test result, equally for CVS and amniocentesis, but the CVS is performed earlier. Whether these subjective improvements outweigh the very real increased risk of miscarriage should be discussed with each patient.

**Aftermath of a Positive Test**

After a positive diagnosis of a chromosomal abnormality, the patient faces the difficult decision of whether or not to terminate the pregnancy. The attitudes and knowledge of the health care provider providing the diagnosis affects the patient’s choice. The patient’s level of education and socio-economic status also plays a role in her decision making. Detection rates do not correlate with termination rates; older women are more likely to continue the pregnancy. Pregnancies with sex chromosome abnormalities (SCA) causing infertility and abnormal sexual development were more likely to be terminated than SCA's that did not affect fertility and sexual development. The lowest termination rates for SCA are for the 47 XYY and 47 XXX karyotypes. Abnormalities visible on ultrasound make the pregnancy less likely to be continued. Overall detection rates are increasing for SCA while termination rates have steadily declined.

**Conclusions**

Second trimester amniocentesis is an effective tool for prenatal genetic diagnosis. Although it is not without risks of serious complications such as miscarriage, it remains the safest technique for prenatal genetic diagnosis. The greatest limitation of second trimester amniocentesis remains the late availability of results, which gives parents little time to make decisions based on the results of the testing. As detection rates of genetic disorders by amniocentesis have increased, termination rates have decreased. Amniocentesis remains a valuable tool for prenatal genetic diagnosis.

**References**


