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Prenatal Diagnosis Procedures and Techniques to Obtain a Diagnostic Fetal Specimen or Tissue: Maternal and Fetal Risks and Benefits

This Clinical Practice Guideline has been prepared by the Genetics Committee and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide maternity care providers and their patients with current evidence-based guidelines for maternal risk/benefit counselling for a prenatally identified at-risk pregnancy that requires ultrasound-guided prenatal diagnostic procedures and/or techniques for a genetic diagnosis and for subsequent pregnancy management decisions on questions such as level of obstetrical care provider, antenatal surveillance, location of care and delivery, and continuation or termination of pregnancy. This guideline is limited to maternal risk/benefit counselling and pregnancy management decisions for women who require, or are considering, an invasive ultrasound-guided procedure or technique for prenatal diagnosis.

Patient population: Pregnant women identified as having an increased risk of a fetal genetic abnormality secondary to the process of established prenatal screening protocols (maternal serum ± imaging, high-risk cell-free DNA results, abnormal diagnostic fetal imaging, or a positive family history of an inherited condition). These women may require or request counselling about pregnancy risks and benefits of an invasive ultrasound-guided procedure to determine the etiology, diagnosis, and/or pathology for the possible fetal anomaly or anomalies.

Evidence: Published literature was retrieved through searches of Medline, PubMed, and the Cochrane Library in and prior to June 2014 using an appropriate controlled vocabulary (prenatal diagnosis, amniocentesis, chorionic villi sampling, cordocentesis) and key words (prenatal screening, prenatal genetic counselling, post-procedural pregnancy loss rate). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies written in English and published from January 1985 to June 2014. Searches were updated on a regular basis and incorporated in the guideline to June 2014. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical speciality societies.

Key words: Prenatal diagnosis, prenatal genetic counselling, prenatal procedure risk, prenatal procedure benefit, amniocentesis, chorionic villi sampling, cordocentesis

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[60]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[60]

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Health benefits, side effects, and risks: Patient informed consent, knowledge translation, genetic prenatal risk assessment, anxiety relief, anxiety creation, advocacy, understanding or limitation for fetal testing, pregnancy management choice, pregnancy complication or loss, timely and improved care for birth of a neonate with recognized morbidity.

Recommendations

1. The health care provider should counsel the at-risk pregnant woman on the different levels of genetic fetal testing in order for her to have a clear understanding and expectation of the level of testing and type of results that are offered. (III-B)
2. As part of the informed consent process, the health care provider should review with the at-risk pregnant woman the risks and benefits of in utero genetic diagnostic techniques associated with fetal genetic testing options. (III-A)
3. During risk/benefit counselling, the health care provider should advise that the best estimate of the pregnancy loss rate related to:
   a. amniocentesis is 0.5% to 1.0% (range 0.17 to 1.53%) (I)
   b. chorionic villus sampling is 0.5% to 1.0% (I) and
   c. cordocentesis or percutaneous umbilical blood sampling is 1.3% for fetuses with no anomalies and 1.3% to 25% for fetuses with single or multiple anomalies or intrauterine growth restriction. (II-2A)

INTRODUCTION

The traditional gold standard prenatal diagnostic results for the fetus are obtained through genetic analysis of pregnancy-related tissues from CVS, AC, or cordocentesis. Currently, maternal serum cfDNA is used for genetic screening, which is followed by traditional prenatal diagnostic techniques when a screen is positive. However, in the future, maternal serum cfDNA may itself come to be used for fetal diagnosis. The risks and benefits for the mother and fetus differ with invasive (traditional) and non-invasive (new) approaches.[1–9]

While the scope of prenatal genetic diagnosis is usually based on the identification of fetal karyotype abnormalities, other analyses of specific genetic mutations are also possible using amniocytes, chorionic villus, or fetal blood. Maternal serum cfDNA molecular technology has potential diagnostic capability, but at the present time is generally restricted to fetal sexing, fetal Rh typing, and screening for trisomies 21, 18, and 13. Other fetal genetic mutations have been identified from maternal serum cfDNA, but only on the basis of a case-by-case genetic differential diagnosis or when a specific family mutation has been identified.

Prenatal diagnostic counselling begins with collecting the patient's family history, ethnic background, past genetic, obstetrical, medical, and surgical history, and the indication for diagnostic fetal testing, and learning about the personal values and needs of the woman and her family. Parental karyotyping may be required for family or personal history of recurrent pregnancy loss or when there is a recognized family history for translocation carrier risks. Molecular genetic testing or referral for genetic assessment may be required when one of the parents presents characteristics suspicious of an undiagnosed genetic syndrome. Maternal and paternal

factors (genetics, family, ethnic, reproductive ages, and personal health history) that may add to the pregnancy risk are summarized in Table 2.[9]

Pre-procedural counselling requires a very clear understanding by both the patient and the provider of the level of genetic testing or diagnosis that is offered or requested. The patient needs a clear explanation, at a level appropriate to her education, literacy, and language skills, of the screening test or fetal anomaly results that have led her to consider prenatal diagnostic fetal testing, so that she can provide informed consent.[9–24] The level and depth of the counselling care and information provided also depend on the expertise of the provider.[1–9]

Once the criteria for offering prenatal invasive testing for an at-risk pregnancy have been met, counselling should include a verbal description, illustrated with diagrams or images, of the most appropriate prenatal procedure for the recommended or required diagnostic genetic testing.

The evidence-based rates for spontaneous (no procedure) pregnancy loss summarized in Table 3 may be used during procedure-related pregnancy loss counselling.[25–34]

Test results and follow-up planning and counselling require a clear description of the time factors related to the diagnostic testing and its results.[22]

This guideline is limited to the genetic diagnostic procedures of CVS, AC, and cordocentesis/PUBS and intended to assist providers in counselling women about targeted fetal genetic testing after a positive obstetrical screening test or the ultrasound identification of fetal anomalies. Routine pregnancy counselling and the offer of prenatal genetic screening have been previously reviewed and published in the SOGC Guideline, "Counselling Considerations for Prenatal Genetic Screening,"[22] and two separate guidelines for obstetrical aneuploidy screening in singleton and twin pregnancies.[23,24]

ABBREVIATIONS

AC	amniocentesis
AF	amniotic fluid
cfDNA	cell-free DNA
CVS	chorionic villus sampling
CSCNV	clinically significant copy number variant
FISH	fluorescence in situ hybridization
PCR	polymerase chain reaction
PUBS	percutaneous umbilical blood sampling
TA	transabdominal
TC	transcervical

Invasive in utero prenatal diagnosis techniques include CVS, AC, PUBS, and fetal tissue sampling (skin, muscle, kidney, liver, ascites, pleural effusion, urine). Some genetic or pathologic diagnostic results may be obtained by more than one technique; for example, fetal karyotype results can be obtained from CVS, AC, and PUBS, but each technique may be provided at different gestational ages.[10–21]

What level of genetic testing analysis does the patient need or want? A risk assessment summary

Maternal and paternal testing need to be specifically directed but are based on past family, ethnic, and obstetrical outcomes history and present pregnancy indications (Table 2).[9]

The available prenatal genetic fetal testing levels must be clear to the patient because they include details ranging from standard or basic to increased levels of molecular complexity. The following levels of testing should be explained:

a. numerical assessment of chromosomes 13, 18, 21, X, and Y by quantitative fluorescence-polymerase chain reaction or FISH;

b. fetal karyotype testing for only the number of chromosomes or chromosome pairs and detection of large chromosome rearrangements, deletions, or duplications;

c. fetal karyotype testing (as in the previous point) with specific directed testing for molecular chromosomal deletions or duplications related to past obstetrical or family history or present fetal anomaly:

   Deletions (interstitial p or q chromosome arm location; terminal and subtelomeric location) should be discussed with examples of their associated anomalies, such as:

   - del(22q11.2) Di George syndrome: cardiac anomaly, thymic hypoplasia, parathyroid dysfunction, cleft palate, distinctive face;
   - del(7q11.23) Williams syndrome: cardiac anomaly, characteristic facies, developmental delay; and
   - del(17p13.3) Miller-Dieker syndrome: cardiac anomaly, omphalocele, joint contractures, characteristic facies.

   Duplications (interstitial, direct "abab" or inverted "abba", and terminal and subtelomeric location) should be discussed, including fetal karyotype (as above) with use of an expanded detailed chromosomal microarray (array genomic hybridization) when fetal anomalies are identified.[35–37]

d. prenatal chromosomal microarray identified clinically relevant deletions or duplications in 1.7% of cases with normal karyotype in a prenatal population with a positive genetic screen (maternal age or positive screen in the1st or 2nd trimester) as the indication for conducting a prenatal karyotype:

Table 2. Taking a pre-conception history for assessment and counselling

GENETIC HISTORY
A thorough pre-conception history identifies couples who are genetically at risk. When women and their partners are informed of the risks of having a baby with birth defects or a genetic disorder prior to pregnancy, they are then able to determine their options regarding a pregnancy (including contraception, gamete donation, adoption, prenatal invasive testing, or chance).
Family history
Construct a three-generation pedigree.
Include assessment of **genetic diseases**, including muscular dystrophy, hemophilia, cystic fibrosis, fragile X syndrome, syndromic congenital heart disease, phenylketonuria, skeletal dysplasia, sickle cell anemia, hemoglobinopathies, and Tay-Sachs disease.
Include assessment of **multifactorial congenital malformations**, such as spina bifida, anencephaly, cleft palate and cleft lip, hypospadias, and congenital heart disease.
Include assessment of **familial diseases with a major genetic component**, such as developmental disability, premature artherosclerosis, diabetes mellitus, psychosis, epileptic disorders, hypertension, rheumatoid arthritis, deafness, and severe refractive disorders of the eye.
Ethnic history
Establish **risks associated with age** (e.g., women under age 15 or over age 35 may carry increased biological risks).
Age
Establish **risks associated with age** (e.g., women under age 15 or over age 35 may carry increased biological risks).
HEALTH HISTORY
Chronic conditions
Assess the presence of chronic conditions that can affect a woman's ability to conceive, as well as the use of medications in treatment of chronic disease and their potential effect on pregnancy such as teratogenicity.
To be considered: diabetes mellitus, anemia, thyroid disorders, gynaecological disorders, hyperphenylalaninemia, asthma, sexually transmitted infections, heart disease, hypertension, deep venous thrombosis, kidney disease, systemic lupus erythematosus, epilepsy, hemoglobinopathies, cancer, seizure disorders, tuberculosis, rheumatoid arthritis, and mental health/psychiatric disorders.
Infectious conditions
Identify women who are **rubella- or varicella**-susceptible. If they are not actively attempting pregnancy, offer a vaccination.
Identify and counsel women at risk for **hepatitis B**. Routine pre-conception testing of all women with hepatitis B is not currently recommended.
Counsel women to avoid exposure to cat feces and raw and undercooked meats. Routine serologic testing for **toxoplasmosis** in the pre-conception period or in pregnancy is not recommended.
Evaluate the woman and her partner for exposure to **sexually transmitted infection** (e.g., chlamydia, HIV, gonorrhea, syphilis).
Reproductive history
Collect information about **menstrual, contraceptive, and sexual histories**; infertility; abnormal Pap smears; and in utero exposure to diethylstilbestrol.
Discuss **past obstetric history**, including early miscarriages; number of pregnancies; type of birth; length of labour; and specific complications, such as premature labour or delivery, gestational diabetes, pregnancy-induced hypertension, and postpartum depression.
Discuss **menstrual difficulties**, specifically excessive cyclic bleeding, amenorrhea, and oligomenorrhea.
Discuss **gynaecological disease**, such as endometriosis and pelvic inflammatory disease.
Lifestyle assessment
Assess lifestyle issues, including nutrition, physical activity, prescription and over-the-counter drug use, other substance use, and environmental exposures, current and past.

Adapted from: Public Health Agency of Canada. Family-centred maternity and newborn care: national guidelines. Chapter 3. Preconception care. Ottawa (ON): Health Canada; 2005.[59]

Table 3. Pre-in utero genetic procedure counselling: estimated background loss etiology and rates for spontaneous pregnancy loss/abortion, clinical miscarriage, or fetal death with no prenatal diagnostic procedure

SA: evidenced-based estimate: 25% to 30%[25–30]
a. Total CM: 25% to 31%. 31% of pregnancies are lost after implantation (< 6 weeks: 18%; 6 to 9 weeks: 4%; > 9 weeks: 3%). CM risk decreases with increasing GA.
b. 80% of SA loss occurs in first trimester (50% chromosomal: 1st trimester 55%; 2nd trimester 35%; 3rd trimester 5%).
c. Total SA loss of conceptions is 50% to 70% (as followed from conception/early implantation).
d. Parental age effect risk:
Maternal age < 20 years: SA = 12%; > 40 years of age: SA = 26%
Paternal age < 20 years: SA 12%; > 40 years of age: SA = 20%
e. Increased parity leads to an increase in SA loss beyond the risk associated with maternal age.
FD/loss rate after 10 gestational weeks: evidenced-based etiology/cause[31–35]
a. Fetal causes: 25% to 40% (chromosomal: birth defect NTD/CNS, cardiac, immune/non-immune hydrops, infection)
b. Placental causes: 25% to 35% (abruption, PROM, implantation/growth issues, chorioamnionitis)
c. Maternal causes: 5% to 10% (diabetes, hypertension, obesity, thyroid, renal, APA, thrombophilia)
d. Unexplained: 15% to 35%

CM: clinical miscarriage; SA: spontaneous abortion; NTD: neural tube defect; CNS: central nervous system; PROM: premature rupture of the membranes; APA: atypical polypoid adenomyoma

This enhanced genetic analysis requires continued directed research during its introduction as part of the routine evaluation. In the same study, the prenatal chromosomal microarray identified an additional 6.0% of cases with a clinically relevant deletion or duplication that was not identified by the standard karyotype when fetal anomalies were the indication for a prenatal karyotype.[36]

Ultrasound-detected fetal anomalies from the NICHD Microarray Trial[36] were analyzed according to the additional microarray genetic pathology and the fetal organ system involved.[37] For the 1082 fetuses with anomalies, 752 had a normal karyotype. Clinically significant copy number variants were present in 61 of the euploid fetuses (8.1%). CSCNVs were present in 13% of fetuses with multiple system anomalies compared with 3.6% of fetuses with no anomalies ($P < 0.001$). For isolated anomalies, the CSCNVs were nominally significant for renal ($P = 0.04$) and cardiac ($P = 0.01$). Other anomalies were small in number and did not meet statistical significance.

e. fetal karyotype with more directed complex or detailed genetic testing because of past reproductive outcome, family history, extended and complex fetal differential diagnosis based on prenatal findings, or personal informed choice:[38–40]

Evaluation data on the use of whole-exome sequencing in pediatric patients with a suspected Mendelian disorder is lending support for the use of this new technology in the prenatal population. In a cohort of 250 children (80% with a neurological phenotype), 86 mutated alleles were found that were highly likely to be causative in 62 of the 250 patients. The result indicated a 25% molecular diagnostic rate (95% CI 20 to 31) with 33 autosomal dominant, 16 autosomal recessive, and 9 X-linked conditions.[39]

f. other directed genetic diagnosis required for familial or parental carrier(s) of autosomal recessive (more common), X-linked, or autosomal diseases[3,4];

g. fetal sexing only limited to X-linked genetic risk assessment.[40]

A prenatal invasive diagnostic procedure counselling checklist (Table 4) has been created to assist the maternity care provider with the primary stages of counselling prior to referral, regional or tertiary centre counselling, and informed consent.

What is the possible etiology for the screen positive result or the structural fetal pathology leading to the consideration of an invasive diagnostic procedure?

Correct gestational dating is required for accurate genetic assessment and evaluation. Butt et al.[8] provided evidence-based recommendations related to the timing (1st and 2nd trimester) of dating ultrasounds.

Ultrasound, ideally performed at 18 to 22 weeks' gestation, is the primary imaging screening and diagnostic tool recommended for fetal anatomy, number, and growth. MRI is used as a second-tier imaging modality, following an abnormal ultrasound; it is usually performed after 22 weeks' gestation.

Major fetal congenital anomalies (malformation, disruption, deformation, dysplasia) occur in an estimated 5% of all live births (3% are identifiable prenatally and 2% at birth or

Table 4. Checklist: reproductive genetics for in utero diagnostic prenatal testing

Name: _____

Date of birth: _____ Maternal age at expected date of delivery: _____

Paternal age at expected date of delivery: _____

Gestations ☐ Term pregnancies ☐ Preterm pregnancies ☐ Spontaneous abortions ☐
Therapeutic abortions ☐ Live births ☐ Stillbirths ☐ Neonatal deaths ☐

Important maternal co-morbidities: _____

Paternal co-morbidities: _____

Family history: _____

Assisted reproductive technology: ☐ yes ☐ no

1. Indication for invasive prenatal testing
   - ☐ Past obstetrical history (fetal chromosomal anomaly/genetic syndrome)
     Specify: _____
   - ☐ Positive family history (translocation carrier; genetic carrier AR/AD/XL inheritance)
     Specify: _____
   - ☐ Positive aneuploidy screening test (first/second trimester positive for nuchal translucency; maternal age > 35)
     Specify: _____
   - ☐ Fetal anomalies identified by ultrasound imaging
     Specify: _____

2. Depth/complexity of fetal testing discussed in patient informed consent counselling
   Genetic complexity, levels I–V
   - ☐ I. Fetal karyotype only (numerical 13, 18, 21, X, Y by QF-PCR or FISH; standard karyotype only)
   - ☐ II. Fetal karyotype plus selected molecular deletion/duplication testing
     Specify molecular deletion/duplication test: _____
   - ☐ III. Fetal karyotype plus array comparative genomic hybridization
   - ☐ IV. Fetal karyotype plus whole genome sequencing
   - ☐ V. Fetal sexing only (molecular/ultrasound)
   - ☐ Other: amniotic fluid testing

3. Procedural risk counselling (procedure and gestational age timing described)
   - ☐ Amniocentesis; pregnancy loss risk 0.5% to 1.0% (range 0.17 to 1.53%)
   - ☐ Chorionic villus sampling: pregnancy loss risk 0.5% to 1.0%
   - ☐ Cordocentesis: pregnancy loss rate with no anomalies 1.3%
     with fetal anomalies 1.3% to 25%

4. Pregnancy management options
   - ☐ Consultation required: obstetrics, maternal-fetal medicine, neonatology, medical genetics
   - ☐ Consultation and transfer of care for delivery required: obstetrics, maternal–fetal medicine
   - ☐ Pregnancy termination (if under consideration)
   - ☐ Continuation of pregnancy (regardless of diagnostic findings)
   - ☐ City and hospital for delivery planning: _____

5. Follow-up post-delivery planning
   - ☐ Autopsy discussion
   - ☐ In-depth reproductive genetic counselling
   - ☐ Pre-conception planning visit recommended

What is the possible etiology for the screen positive result or the structural fetal pathology leading to the consideration of an invasive diagnostic procedure?

AR: autosomal recessive; AD: autosomal dominant; XL: X-linked; QF-PCR: quantitative fluorescence-polymerase chain reaction

during the first year of life, as some anomalies will have a functional component with no obvious structural change). Minor structural anomalies are becoming more identifiable with improved ultrasound technology, allowing for more detailed facial, CNS, and cardiac imaging.

The most commonly recognized etiologies for fetal anomalies are chromosomal abnormalities, teratogenic exposure (drugs, chemical, infectious), maternal co-morbidities (maternal age > 35 years, diabetes, epilepsy, hypertension), deformations or disruptions (structural uterine anomalies, oligohydramnios, monochorionic twinning abnormalities) and placental abnormalities.[2,5–7] Confined placental mosaicism is normally present in 1% to 2% of placentas, where it is limited to the placenta and the fetus is chromosomally numerically normal but may have a genetic anomaly such as uniparental disomy. This placental and embryonic biological discordance will have a possible impact on invasive CVS trophoblastic analysis. True fetal mosaicism is rare, so AC will sometimes, be affected, but minimally.[41]

The pregnant woman identified to have an aneuploidy screen positive result or an ultrasound with a fetal anomaly or anomalies requires reproductive genetic counselling so that she has a clear understanding of her a priori risk assessment for fetal pathology and outcome, which will allow her to make an informed choice in regard to in utero diagnostic testing (Tables 2 to 4).

Recommendation

1. The health care provider should counsel the at-risk pregnant woman on the different levels of genetic fetal testing in order for her to have a clear understanding and expectation of the level of testing and type of results that are offered. (III-B)

Techniques 101: for patient and family risk counselling and discussion of technique

All of the in utero diagnostic techniques (AC, CVS, PUBS)[10–20] are done under continuous ultrasound guidance, thereby minimizing any unintended fetal damage or injury. Prophylactic antibiotics are not required for the procedure. Patients are recommended to consider decreased physical activity for 12 to 24 hours after the procedure, but bed rest is not required.

The in utero prenatal diagnosis techniques of AC and CVS are used for both singleton and twin pregnancies, and PUBS is used in singleton and dichorionic twin pregnancies.

AC is the most common in utero prenatal testing technique, and it is recommended for use after 15 weeks' gestation, usually with a 22-gauge spinal needle with stylet to obtain the specimen of AF. During AC, placental puncture with the needle should be avoided if possible. Sterile technique is recommended, with the use of abdominal antiseptic cleaning, gloves, sterile drapes, and a sterile ultrasound probe cover. Maternal local anaesthetic is not usually required. A single needle is usually inserted, and the AF volume removed is 15 to 25 cc depending on the fetal testing required. Testing is usually from amniocytes (fetal origin from skin or bladder) for chromosome analysis and from protein, biochemical, or enzymatic analysis of the AF supernatant. Results are usually available after 1 to 3 weeks. Spotting, bleeding, or fluid leakage after AC is estimated at 1% to 5% and is usually limited with decreased activity.[10–17,20,40–49]

Early AC at 12 to 15 weeks' gestation is **not** recommended due to an increased risk of pregnancy loss and fetal talipes (club foot) secondary to temporary or intermittent oligohydramnios.[10]

CVS is the recommended first trimester in utero technique. TCCVS (at 10 to 13+6 weeks' gestation) is an ultrasound-guided technique using a flexible catheter and syringe suction or metal biopsy forceps to obtain placental tissue. TACVS (at 10 to 36 weeks' gestation) is an ultrasound-guided technique using an 18- to 20-gauge needle and syringe suction to obtain the placental tissue. Because of the larger needle gauge used in TACVS and the aspirating needle movement within the placenta, local anaesthesia may be required depending on patient need. Karyotype results and time to result availability are similar using either approach. TCCVS has an estimated post-procedural risk of vaginal spotting or minimal bleeding of 10% to 20%, while TACVS has more post-procedural uterine discomfort and cramping.[10–13,17,18,20,43,49–56]

Four Cochrane systematic reviews have evaluated various aspects of the invasive prenatal diagnosis techniques:

Alfirevic et al.[15] concluded that "second trimester amniocentesis is safer than early amniocentesis or transcervical CVS, and is the procedure of choice for second trimester testing. Transabdominal CVS should be regarded as the procedure of first choice when testing before 15 weeks gestation. Diagnostic accuracy of different methods could not be assessed adequately because of incomplete karyotype data in most studies."

Mujezinovic and Alfirevic[52] concluded that "in general, women that undergo amniocentesis could be informed that pain during the procedure is minor and that there is currently insufficient evidence to support the use of local anaesthetics, leg rubbing or subfreezing the needle for pain reduction during procedure."

Mujezinovic and Alfirevic[43] examined technique variations or modifications for reducing the risks from AC or CVS, and found that, "in the absence of clear evidence, the operators should continue to use methods and technique modifications with which they are most familiar".

Young et al.[51] concluded that "for transcervical CVS, the evidence is not strong enough to support a change in practice for clinicians who have become familiar with a particular technique. Based on current evidence, there is no difference in clinically important outcomes with the use of a continuous compared with a discontinuous negative pressure needle aspiration system."

Cordocentesis or PUBS is usually performed after 18 weeks' gestation and is used for both fetal diagnosis and fetal therapy (intrauterine fetal transfusion). It is a continuous ultrasound-guided technique with a 20- to 22-gauge needle being directed, preferentially, into the umbilical cord vein. Puncture of the umbilical artery can cause umbilical arterial constriction with possible fetal cardiac dysfunction. Needle puncture sites are variable and depend upon the provider's preference at the fixed placental umbilical cord insertion site, the fetal intrahepatic vein, or a free loop of umbilical cord usually pinned against the fetus, placenta, or uterine wall to allow venipuncture. A recent systematic review of the technique[19] details the risks and benefits of this technique usually offered by trained and experienced providers.

Invasive prenatal diagnosis technique: risk/benefit summaries

Table 5 summarizes risk/benefit studies of AC.

Additional risk details for AC include:

- procedure-related loss difference with maternal age > 35 years[14]:
  - < 24 weeks 0.17% (0.37; 0.20)
  - < 28 weeks 0.50% (1.37; 0.87)
- singleton loss rates[49]:
  - total post amniocentesis pregnancy loss: 1.9% (1.4 to 2.5)
  - pregnancy loss < 24 weeks post/amniocentesis: 1.3% (1.0 to 1.7)
- total post-procedural rates[17] of:
  - miscarriage: 1.2% to 1.5%
  - intrauterine death: 0.5% to 0.9%
  - termination: 2.5% to 5.7%
  - live birth: 92.1% to 95.5%
- maternal age at procedure and total post-procedural loss rates[17]:
  - age < 30: 1.5%
  - age 30 to 34: 1.3%
  - age > 34: 1.4%
- twin loss rates[49]:
  - total post AC pregnancy loss: 3.07% (1.83 to 4.61)
  - pregnancy loss < 24 weeks post AC: 2.54% (1.43 to 3.96)

Table 6 summarizes risk/benefit studies of CVS.[23–26,30,31,33,42,48–56]

Additional details of CVS risk include:

- singleton loss rates:[49]
  - total post CVS pregnancy loss: 2.0% (1.4 to 2.6)
  - pregnancy loss rate < 20 weeks post CVS: 0.8% (0.2 to 1.7)
  - pregnancy loss rate < 24 weeks post CVS: 1.3% (amnio 0.9%)
- total post procedure rates[17] of:
  - miscarriage: 1.6% to 2.4%
  - intrauterine death: 0.4% to 0.5%
  - termination: 3.8% to 10.1%
  - live birth: 87.6% to 94.3%
- maternal age at procedure and total post procedure loss rates:
  - age < 30: 1.5%
  - age 30 to 34: 1.7%
  - age > 34: 2.0%

CVS operator experience and safety improved with higher annual numbers and combined TA/TC experience versus TC alone.[53]

Significantly increased TCCVS post-procedural pregnancy loss rates and complications are associated with the number of cervical passages: > 1 pass, OR for loss is 3.96 ($P = 0.01$) and for complication is 2.76 ($P = 0.02$)[54]

- twin loss rates[49]:
  - total post CVS pregnancy loss: 3.84% (2.48 to 5.47)
  - pregnancy loss < 20 weeks: 2.75% (1.28 to 4.75)

The relative risk for CVS technique in twins (TA > TC) is 2.08 (0.73 to 5.91; total fetal loss: TA 7.09% [10/141] and TC 3.94% [5/127]).[55,56]

Table 5. Amniocentesis procedure[10–17,20,43–50]

Indications: increased risk of fetal chromosomal or genetic pathology based on previous obstetrical or family history, maternal age, positive aneuploidy screening test, single or multiple major congenital anomalies, parental chromosomal translocation carrier	**Singleton**	**Twin**
Gestational age range: second and third trimesters (Early amniocentesis at 12 to 15 weeks is not acceptable care.)	≥ 15 to 38 weeks' gestation Overall distribution of gestational age at the time of amniocentesis from a 32 852 cohort (1996–2006)[17] • < 15 weeks (21.6%) • ≥ 15 weeks (78.4%)	≥ 15 to 38 weeks' gestation
Risk of miscarriage above the estimated background rate or as the loss rate (total or at a specific GA beyond procedural related affect, related to maternal age, GA at procedure, indication for procedure, provider experience)	Estimated total singleton procedure loss risk is 0.5% to 1.0% (range 0.17 to 1.5%) Single RCT[45]: Total pregnancy loss difference post-procedure was 1.0% (95% CI 0.3 to 1.5%) **Post-amniocentesis loss rate** (1.7%) versus spontaneous loss rate with no amniocentesis (0.7%) Cohort summary[16]: Pregnancy loss attributable to amniocentesis procedure: 0.6 to 1.0% (range 0.19 to 1.53%)	Estimated "attributable" twin procedure risk[46–48]: • twin amniocentesis 2.7% • twin no amniocentesis 0.6% Systematic review[20] Pregnancy loss (23/632) • OR 3.07% (95% CI 1.83 to 4.61) Fetal loss (87/1741) • OR 4.14% (95% CI 1.91 to 7.15) Meta-analysis of 2026 twin pregnancies with amniocentesis[49] • OR 2.42% (95% CI 1.24 to 4.74) Procedure loss with chorionicity separation is very limited with no defined estimation
Fetal anomaly disruptive risk	No risk	No risk
Probability of successful procedure (counselling point)	With a skilled provider > 99%, unless chorion-amnion separation occurs	> 99% But possible difference for MC and DC twins
Time to laboratory diagnosis	Standard time for rapid < 24 hrs and culture in 1 to 3 weeks	Standard time for rapid < 24 hrs and culture in 1 to 3 weeks
Accuracy (chromosomes/aneuploidy/translocation)	Highly accurate for large chromosomal pathology	Highly accurate for large chromosomal pathology
Other lab-based testing		
Microarray	Yes	Yes
Whole genome sequencing	Yes	Yes
Lab-based findings		
Mosaicism	True fetal mosaicism is rare	True fetal mosaicism is rare
AFP	Possible	Possible
AChE	Possible	Possible
Other	Other AF products from fetal urine and respiratory sources can be measured	Other AF products from fetal urine and respiratory sources can be measured
Other post procedural risks	AF leakage: talipes at 15 to 16 weeks: 1.7%–2.4% to 0.2%–0.8% (early amniocentesis at 12 to 15 weeks is no longer acceptable care.)	Background "no procedure" loss rate for twins is estimated to be higher than for singletons; probable background chorionicity loss rate is higher in MC than DC.

AFP: alpha-fetoprotein; AChE: acetylcholinesterase; MC monochorionic; DC: dichorionic; AF: amniotic fluid

Table 6. CVS (TA/TC) procedures

Indications: increased risk of fetal chromosomal or genetic pathology based on previous obstetrical or family history, maternal age, positive aneuploidy screening test, single or multiple major congenital anomalies, parental chromosomal translocation carrier	**Singleton**	**Twins** (MC/DC)
Gestational age range: first to third trimester	TA: 10 to 32 weeks TC: 10 to 11+6 weeks	TA: 10 to 32 weeks TC: 10 to 11+6 weeks
Risk of miscarriage: above the estimated background rate or as the loss rate (total or at a specific GA beyond procedure-related effects) related to maternal age, GA at procedure, indication for procedure, provider experience	Estimated added post-procedure loss rate is 0.5% to 1.0% or total spontaneous and procedure loss rate is 1.9% to 2.0% Estimated added risk[57]: Total fetal loss rate for TA CVS = second trimester amniocentesis rate RR 0.9 (95% CI 0.66 to 1.23): TA: 1% to 2% TC: 2% to 6% TC increased fetal loss by OR 1.40 (95% CI: 1.09 to 1.81).	Background spontaneous pregnancy and fetal loss rate is increased for twins. Twin systematic review[33] post procedure: Total pregnancy loss: OR 3.84% (95% CI 2.48 to 5.47) Total fetal loss: OR 5.48% (95% CI 4.06 to 7.13)
Risk of congenital fetal disruptive anomaly	Limb reduction < 9 weeks (66 days) (estimated at 1 in 3000) possible hemangioma	Limb reduction < 9 weeks (66 days) (estimated at 1 in 3000) possible hemangioma
Probability of successful procedure	With a skilled provider > 99% with combination of both TC and TA techniques or approach	> 99% with combination of both TC and TA techniques and/or approach
Time to laboratory diagnosis	2 to 3 weeks (rapid direct FISH/PCR techniques can be used as required)	2 to 3 weeks (rapid direct FISH/PCR techniques can be used as required)
Accuracy (chromosomes/aneuploidy/translocation)	Highly accurate for large chromosomal pathology	Highly accurate for large chromosomal pathology
Other lab based testing		
microarray	Yes	Yes
whole genome sequencing	Yes	Yes
Lab-based findings		
Mosaicism	Confined to placenta; 1% to 2%	Confined to placenta; 1% to 2%
AFP	No	No
AChE	No	No
Other	Placenta-based genetic/biochemistry/enzyme	Placenta-based genetic/biochemistry/enzyme
Other procedural risk	There is no preeclampsia-induced or -associated risk with CVS. The first-trimester placental analytes result in screen positive results that require diagnostic testing by CVS.	

RR: relative risk

Table 7. Risk/benefit data for cordocentesis/PUBS[32]

Indications: suspected fetal anemia; NAIT; NIH; aneuploidy; fetal Bg platelets; genetic analysis (mutation, biochemistry); fetal therapy	PUBS is generally used for **singleton** fetal blood sampling only	
Gestational age range	18 to 24 weeks	22-gauge needle (smaller)
	> 24 weeks	20-gauge needle
Total risk of miscarriage	**18 to 24 weeks increased risk** No anomalies: 1% Anomalies: 7% IUGR: 14% Hydrops: 25%	**Consensus** No anomalies: 1.3% Fetal pathology: > 1.3%
Fetal anomaly disruptive risk	Increased risk if sustained bleeding from cord with significant anemia and/or hypotension	
Probability of successful procedure (counselling points)	With a skilled provider, greater than 98% A small specimen can be confirmed in the lab to be fetal blood through testing for red blood cell MCV or Kleihauer-Betke criteria. The best fetal vessel locations or sources the provider may choose from are the intra-hepatic vein, the fetal abdominal cord insertion site, the free cord loop, or fetal cardiac ventricule (right or left).	
Time to laboratory diagnosis	Based on hematologic, biochemical, or genetic testing requested but similar to neonatal results	
Accuracy (chromosomes) aneuploidy/translocation	Highly accurate for large chromosomal pathology	
Other lab-based testing		
Microarray	Highly accurate: additive genetic information with standard normal karyotype[36] With advanced maternal age and/or positive screen 1.7% With structural anomaly 6.0%	
Whole genome sequencing	Provides detailed genetic mutational information	
Lab-based findings		
Mosaicism (bone marrow)	Accurate but based on chromosomal mosaicism, %	
AFP	Yes, if required	
AChE	Yes, if required	
Other	any neonatal blood parameters	
Other procedural risks		**Procedural protocol technical aspects**
Umbilical cord bleeding	20% to 30%	Antibiotics
Fetal bradycardia	5% to 10%	Maternal sedation
Vertical infection (hepatitis B or C; HIV) through maternal-to-fetal circulation	Unknown, but estimated to be low	Local anaesthesia Skin preparation Needle guidance Needle gauge and length Paralytic agent Sampling site

NAIT: neonatal alloimmune thrombocytopenia; NIH: neonatal intraventricular hemorrhage; Bg: human leukocyte antigens class I; IUGR intrauterine growth restriction; MCV: mean corpuscular volume

The data available for cordocentesis/PUBS is presented in Table 7. The introduction of non-invasive prenatal testing for fetal trisomy screening in low-risk (no added history or pregnancy-related risk) and high-risk (obstetrical screen positive or maternal age) populations will decrease the number of invasive procedures requested or required. This impact will be primarily on AC and CVS. This decrease in procedures will impact training and maintenance of skills for invasive procedure providers.[58]

Recommendations

2. The health care provider should counsel the at-risk pregnant woman with regards to the in utero genetic diagnosis techniques(s) associated with the fetal genetic testing options, and review the risks/benefits as part of the informed consent process. (III-A)
3. During risk/benefit counselling, the health care provider should advise that the best estimate of the pregnancy loss rate related to:
   a. amniocentesis is 0.5% to 1.0% (range 0.17 to 1.53%) (I)
   b. chorionic villus sampling is 0.5% to 1.0% (I) and
   c. cordocentesis or percutaneous umbilical blood sampling is 1.3% for fetuses with no anomalies and 1.3% to 25% for fetuses with single or multiple anomalies or intrauterine growth restriction. (II-2A)

SUMMARY

Risk/benefit counselling for in utero prenatal diagnosis procedures requires appropriate patient information with fetal-specific genetic depth of analysis and level of testing recommended to assist in the informed consent process.

Cost-effectiveness analysis (of medical, personal, and genetic information) are not yet available for these new prenatal diagnosis scenarios. Patient choice and consent will require new counselling processes and time commitments.

Prenatal in utero diagnostic procedures are considered to be relatively safe, but they do have a small added pregnancy loss risk over the natural or spontaneous pregnancy fetal loss rate.

The field is rapidly evolving, and SOGC, like other health organizations, will endeavour to stay abreast of evidence as it becomes available.

REFERENCES

1. Langlois S, Wilson RD; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent. SOGC Clinical Practice Guideline, No. 177, April 2006. J Obstet Gynaecol Can 2006;28:324–32.
2. Wilson RD; SOGC Genetics Committee; SOGC Infectious Disease Committee. Principles of human teratology: drug, chemical and infectious exposure. SOGC Clinical Practice Guideline, No. 199, November 2007. J Obstet Gynaecol Can 2007;29:911–7.
3. Langlois S, Ford JC, Chitayat D; CCMG Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Carrier screening for thalassemia and hemoglobinopathies in Canada. Joint SOGC–CCMG Clinical Practice Guideline, No. 218, October 2008. J Obstet Gynaecol Can 2008;30:950–9.
4. Chitayat D, Wyatt PR; Society of Obstetricians and Gynaecologists of Canada Genetics Committee; Canadian College of Medical Geneticists Prenatal Diagnosis Committee. Fragile X testing in obstetrics and gynaecology in Canada. Joint SOGC–CCMG Committee Opinion, No. 216, September 2008. J Obstet Gynaecol Can 2008;30:837–41.
5. Gagnon A; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada. Evaluation of prenatally diagnosed structural congenital anomalies. SOGC Clinical Practice Guidelines, No. 234, September 2009. J Obstet Gynaecol Can 2009;31:875–81.
6. Lausman A, Kingdom J; Society of Obstetricians and Gynaecologists of Canada Maternal Fetal Medicine Committee. Intrauterine growth restriction: screening, diagnosis and management. SOGC Clinical Practice Guidelines, No. 295, August 2013. J Obstet Gynaecol Can 2013;35:741–8.
7. Desilets V, Audibert F; Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Investigation and management of non-immune fetal hydrops. SOGC Clinical Practice Guidelines, No. 297, October 2013. J Obstet Gynaecol Can 2013;35:923–36.
8. Butt K, Lim K; Society of Obstetricians and Gynaecologists of Canada Diagnostic Imaging Committee. Determination of gestational age by ultrasound. SOGC Clinical Practice Guidelines, No. 303, February 2014. J Obstet Gynaecol Can 2014;36:171–81.
9. Wilson RD; Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Genetic considerations for a woman's pre-conception evaluation. SOGC Committee Opinion, No. 253, January 2011. J Obstet Gynaecol Can 2011;33:57–64.
10. Simpson JL. Invasive procedures for prenatal diagnosis: any future left? Best Pract Res Clin Obstet Gynaecol 2012;26:625–38.
11. Collins LS, Impey L. Prenatal diagnosis: types and techniques. Early Hum Dev 2012;88:3–8.
12. Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. Fetal Diagn Ther 2010;27:1–7.
13. Dugoff L, Hobbins JC. Invasive procedures to evaluate the fetus. Clin Obstet Gynecol 2002;45:1039–53.
14. Pitukkijronnakorn S, Promsonthi P, Panburana P, Udomsubpayakul U, Chittacharoen A. Fetal loss associated with second trimester amniocentesis. Arch Gynecol Obstet 2011;284:793–7.
15. Alfirevic Z, Mujezinovic F, Sundberg K. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2003;3:CD003252.
16. Wilson RD, Langlois S, Johnson J; SOGC Genetics Committee; CCMG Prenatal Diagnosis Committee. Mid-trimester amniocentesis fetal loss rate. SOGC Clinical Practice Guidelines, No. 194, June 2007. J Obstet Gynaecol Can 2007;29:586–90.
17. Tabor A, Vestergaard CHF, Lidegaard O. Fetal loss rate after chorionic villus sampling and amniocentesis: an 11-year national registry study. Ultrasound Obstet Gynecol 2009;34:19–24.
18. Basaran A, Basaran M, Topatan B. Chorionic villus sampling and the risk of preeclampsia: a systematic review and meta-analysis. Arch Gynecol Obstet 2011;283:1175–81.
19. Berry SM, Stone J, Norton ME, Johnson D, Berghella V. Fetal blood sampling. Am J Obstet Gynecol 2013;209:170–80.
20. Agarwal K, Alfirevic Z. Pregnancy loss after chorionic villus sampling and genetic amniocentesis in twin pregnancies: a systematic review. Ultrasound Obstet Gynecol 2012;40:128–34.
21. Vink J, Fuchs K, D'Alton ME. Amniocentesis in twin pregnancies: a systematic review of the literature. Prenat Diagn 2012;32:409–16.

22. Cartier L, Murphy-Kaulbeck L; Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Counselling considerations for prenatal genetic screening. SOGC Committee Opinion, No. 277, May 2012. J Obstet Gynaecol Can 2012;34:489–93.
23. Chitayat D, Langlois S, Wilson RD; Society of Obstetricians and Gynaecologists of Canada Genetics Committee; Canadian College of Medical Geneticists Prenatal Diagnosis Committee. Prenatal screening for fetal aneuploidy in singleton pregnancies. Joint SOGC-CCMG Clinical Practice Guideline, No. 261, July 2011. J Obstet Gynaecol Can 2011;33:736–50.
24. Audibert F, Gagnon A, Wilson RD, Blight C, Brock JA, et al. Prenatal Screening for and Diagnosis of Aneuploidy in Twin Pregnancies. J Obstet Gynaecol Can 2011;33(7):754–67.
25. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319:189–94.
26. Fantel AG, Shepart TH, Vadheim-Roth C, Shepard TH, Coleman C. Embryonic and fetal phenotypes: prevalence and other associated factors in a large study of spontaneous abortion. In: Porter IH, Hook EM, editors. Human embryonic and fetal death. New York (NY): Academic Press; 1980, p. 71.
27. Wilson RD, Kendrick V, Wittmann BK, McGillivray B. Spontaneous abortion and pregnancy outcome after normal first-trimester ultrasound examination. Obstet Gynecol 1986;67:352–5.
28. Wijesiriwardana A, Bhattacharya S, Shetty A, Smith N, Bhattacharya S. Obstetric outcome in women with threatened miscarriage in the first trimester. Obstet Gynecol 2006;107:557–62.
29. Eiben B, Bartels I, Bähr-Prosch S, Borgmann S, Gatz G, Gellert G, et al. Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. Am J Hum Genet 1990;47:656–63.
30. Schrek R, Silverman N. Chapter 37: fetal loss. In: Rimoin DL, Connor JM, Pyretz RE, Kork BR. Emery and Rimoin's principles and practice of medical genetics. 3rd ed. Edinburgh (GB): Churchill Livingstone; 2002, pp. 983–5.
31. Cunningham FG, Hollier LM. Chapter 29: categories and causes of fetal death in diseases and injuries of the fetus and newborn. In: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY, editors. Williams obstetrics, 23rd ed. New York (NY): McGraw Medical; 1997, p. 631.
32. Eller AG, Branch DW, Byrne JL. Stillbirth at term. Obstet Gynecol 2006;108:442–7.
33. Reddy UM. Predication and prevention of recurrent stillbirth. Obstet Gynecol 2007;110:1151–64.
34. Silver RM. Fetal death. Obstet Gynecol 2007;109:153–67.
35. Duncan A, Langlois S; SOGC Genetics Committee; CCMG Prenatal Diagnosis Committee. Use of array genomic hybridization technology in prenatal diagnosis in Canada. SOGC–CCMG Joint Technical Update, No. 270, December 2011. J Obstet Gynaecol Can 2011;33:1256–9.
36. Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med 2012;367:2175–84.
37. Donnelly JC, Platt LD, Rebarber A, Zachary J, Grobman WA, Wapner RJ. Association of copy number variants with specific ultrasonographically detected fetal anomalies. Obstet Gynecol 2014;124:83–90.
38. Talkowski ME, Ordulu Z, Pillalamarri V, Benson CB, Blumenthal I, Connolly S, et al. Clinical diagnosis by whole-genome sequencing of a prenatal sample. N Engl J Med 2012;367:2226–32.
39. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, et al. Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. N Engl J Med 2013;369:1502–11.
40. Van den Hof M, Demiancziuk N, Bly S, Gagnon R, Lewthwaite B, et al. Fetal sex determination and disclosure. J Obstet Gynaecol Can 2007;29:368
41. Wilson RD; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada. Amended Canadian guideline for prenatal diagnosis (2005) - techniques for prenatal diagnosis. SOGC Clinical Practice Guidelines, No. 168, November 2005. J Obstet Gynaecol Can 2005;27:1048–54.
42. Nizard J. Amniocentesis: technique and education. Curr Opin Obstet Gynecol 2010;22:152–4.
43. Mujezinovic F, Alfirevic Z. Technique modifications for reducing the risks from amniocentesis or chorionic villus sampling (review). Cochrane Database Syst Rev 2012;8:CD008678.
44. Tabor A, Madsen M, Obel E, Philip J, Bang J, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986;1:1287–93.
45. Jenkins TM, Wapner RJ. The challenge of prenatal diagnosis in twin pregnancies. Curr Opin Obstet Gynecol 2000:12:87–92.
46. Yukobowich E, Anteby EY, Cohen SM, Lavy Y, Granat M, Yagel S. Risk of fetal loss in twin pregnancies undergoing second trimester amniocentesis. Obstet Gynecol 2001;98:231–34.
47. Cahill AG, Macones GA, Stamilio DM, Dicke JM, Crane JP, Odibo AO. Pregnancy loss rate after mid-trimester amniocentesis in twin pregnancies. Am J Obstet Gynecol 2009;200:257.e1–e6.
48. Millaire M, Bujold E, Morency AM, Gauthier RJ. Mid-trimester genetic amniocentesis in twin pregnancy and the risk of fetal loss. J Obstet Gynaecol Can 2006;28:512–8.
49. Mujezinovic F, Alfirevic Z. Procedure-related complications of amniocentesis and chorionic villous sampling: a systematic review. Obstet Gynecol 2007;110:687–94.
50. Blumenfeld YJ, Chueh J. Chorionic villus sampling: technique and training. Curr Opin Obstet Gynecol 2010;22:146–51.
51. Young C, von Dadelszen P, Alfirevic Z. Instruments for chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2013;1:CD000114.
52. Mujezinovic F, Alfirevic Z. Analgesia for amniocentesis or chorionic villus sampling. Cochrane Database Syst Rev 2011;11:CD008580.
53. Lim K, Omidakhsh N, Hutcheon J, Lee B, Gong J, Gagnon A, et al. Abstract 141: CVS loss and complication rates: operator dependent factors. 34th Annual Society of Maternal Fetal Medicine Meeting. Amer J Obstet Gynecol 2014;210(1 Suppl):S84. (Abstract)
54. Lim K, Omidakhsh N, Hutcheon J, Lee B, Gong J, Gagnon A, et al. Abstract 142: Technical factors contributing to procedure-related loss and complication rates following transcervical chorionic villus sampling. 34th Annual Society of Maternal Fetal Medicine Meeting. Amer J Obstet Gynecol 2014;210(1 Suppl):S85. (Abstract)
55. De Catte L, Liebaers I, Foulon W, Bonduelle M, Van Assce E. First trimester chorionic villus sampling in twin gestations. Am J Perinatol 1996;13:413–7.
56. De Catt L, Liebears I, Foulon W. Outcome of twin gestations after first trimester chorionic villus sampling. Obstet Gynecol 2000;96;714–20.
57. Alfirevic Z, Sundberg K, Brigham S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2003;(3):CD003252.
58. Langlois S, Brock JA; Genetics Committee of the Society of Obstetrics and Gynaecology Canada. Current status in non-invasive prenatal detection of Down syndrome, trisomy 18, and trisomy 13 using cell-free DNA in maternal plasma. SOGC Committee Opinion, No. 287, February 2013. J Obstet Gynaecol Can 2013;35:177–81.
59. Public Health Agency of Canada. Family-centred maternity and newborn care: national guidelines. Chapter 3. Preconception care. Ottawa (ON): Health Canada; 2005.
60. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canad ian Task Force on Preventive Health Care. CMAJ 2003;169:207–8.