Abstract

Objective: To develop a Canadian consensus document with recommendations on maternal screening for fetal aneuploidy (e.g., Down syndrome and trisomy 18) in pregnancy.

Options: Pregnancy screening for fetal aneuploidy started in the mid 1960s, using maternal age as the screening test. New developments in maternal serum and ultrasound screening have made it possible to offer all pregnant patients a non-invasive screening test to assess their risk of having a fetus with Down syndrome or trisomy 18 to determine whether invasive prenatal diagnosis tests are necessary. This document will review the options available for non-invasive screening and make recommendations for Canadian patients and health care workers.

Outcomes: To offer non-invasive screening for Down syndrome or trisomy 18 to all pregnant women. Invasive prenatal diagnosis would be limited to women who screen above a set risk cut-off level on non-invasive screening or pregnant women who will be 40 years at time of delivery who, after counselling, chose to go directly to amniocentesis/chorionic villi sampling (CVS). Currently available non-invasive screening options include maternal age combined with (1) first trimester screening (FTS) (nuchal translucency, maternal serum biochemical markers); (2) second trimester serum screening; or (3) two-step integrated screening, which includes first and second trimester serum screening with or without nuchal translucency (IPS, Serum IPS, contingent and sequential). These options are reviewed and recommendations are made.

Evidence: A MEDLINE search was carried out to identify papers related to this topic that were published between 1982 and 2006. Practices across Canada were surveyed. A consensus document was drafted and reviewed by committee members.

Values: The quality of evidence and classification of recommendations followed discussion and consensus by the combined committees of SOGC (Genetics, Diagnostic Imaging) and CCMG (Prenatal Diagnosis).

Benefits, Harms, Costs: These guidelines are intended to reduce the number of amniocenteses done when maternal age is the only indication. This will have the benefit of reducing the numbers of normal pregnancies lost because of complications of invasive procedures. Any screening test has an inherent false positive rate, which may result in undue anxiety. A detailed cost-benefit analysis of the implementation of this guideline has not been done, since this would require health surveillance and research and health resources not presently available; however, these factors need to be evaluated in a prospective approach by provincial and territorial initiatives.

Key Words: Placenta previa, placenta accreta, management, prenatal diagnosis, ultrasound, Caesarean section, transvaginal sonography, low-lying placenta
Recommendations

1. All pregnant women in Canada, regardless of age, should be offered, through an informed consent process, a prenatal screening test for the most common clinically significant fetal aneuploidies in addition to a second trimester ultrasound for dating, growth, and anomalies. (I-A)

2. Maternal age screening is a poor minimum standard for prenatal screening for aneuploidy and should be removed as an indicator for invasive testing. Amniocentesis/chorionic villi sampling (CVS) should not be provided without multiple marker screening results except for women over the age of 40. Patients should be counselled accordingly. (I-A)

3. In 2007, as a minimum standard, any prenatal screen offered to Canadian women should have a 75% detection rate with no more than a 5% false positive rate for Down syndrome. The performance of the screen should be substantiated by annual audit. (III-B)

4. First trimester nuchal translucency should be interpreted for risk assessment only when performed by sonographers/sonologists trained and accredited to provide this service and with ongoing quality assurance. (II-2A) It should not be offered as a screen without biochemical markers except in the context of multiple gestation pregnancies. (I-A)

5. For women who undertake first trimester screening (FTS), second trimester serum alpha fetoprotein (AFP) screening and/or ultrasound examination is recommended to screen for open neural tube defect (ONTD). (II-1A)

6. First trimester screening (FTS), the first step of integrated screening (with or without nuchal translucency), contingent, and sequential screening are performed in an early and relatively narrow time window. Timely referral is critical to ensure women are able to undergo the type of screening test they have chosen. (II-1A)

7. Soft markers or anomalies in the 18- to 20-week ultrasound can be used to modify the a priori risk of aneuploidy established by age or prior screening provided the scan is undertaken in an established centre performing tertiary level ultrasound. In the absence of ultrasound soft markers or anomalies, a negative likelihood ratio of 0.5 should be used. (II-2B) Evaluation of the fetal nasal bone in the first trimester remains technically difficult and should not be incorporated as a screen until locally established as an effective risk assessment tool. (IIIB)

8. Health care providers should be aware of the screening modalities available in their province or territory. (III-B)

9. Screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding to adjust the program to new technology and protocols. (II-B)

10. Screening programs should show respect for the needs and quality of life of persons with disabilities. Counselling should be nondirective and should respect a woman’s choice to accept or to refuse any or all of the testing or options offered at any point in the process. (III-I)

11. By 2008, screening programs should aim to provide a screen that, as a minimum, offers women who present in first trimester a detection rate of 75% for Down syndrome, with no more than a 3% false positive rate. (II-B)


INTRODUCTION

Screening for chromosomal anomalies and open neural tube defects (ONTDs) is part of prenatal care offered to all Canadian women. Since the methods of screening for ONTDs have not changed since the mid-1970s, they will not be discussed here. Screening for ONTDs in Canada requires second trimester serum alpha fetoprotein (AFP) (16–20 completed weeks) and/or ultrasound examination done at 18 to 22 weeks of gestation.

Screening for fetal chromosomal anomalies, including Down syndrome, began with amniocentesis in the mid-1960s. At that time, the criterion for screening was maternal age. In Canada, screening was offered only to women 35 years or over at the expected date of delivery. This was determined to be the point at which the risk of causing the loss of a pregnancy was less than the chance of identifying a pregnancy with a significant chromosome disease. This clinical practice guideline reviews the evolution of screening for fetal aneuploidy from screening using maternal age alone to the many options currently available and makes recommendations regarding the minimum standard of prenatal screening that should be available to all Canadian women. The level of evidence and quality of recommendations are described using the criteria and classifications of the Canadian Task Force on Preventive Health Care (Table 1).

WHAT IS SCREENING?

Screening is the process of surveying a population, using a specific marker or markers and defined screening cut-off levels, to identify the individuals in the population at higher risk for a particular disorder. Screening is applicable to a population; diagnosis is applied at the individual patient level.2

Screening for a disorder should be undertaken only when the disorder is considered to be serious enough to warrant intervention. The marker(s) used in screening must be able to identify a significant proportion of affected persons with minimal misidentification of unaffected persons. There must also be both a highly accurate diagnostic test to determine whether the person with a screen positive result truly has the disorder and an intervention available to all persons who are identified as being affected. The screen, including follow-up testing and intervention, must be affordable. Finally, the screen must be acceptable to the population being screened.

The screening procedure should not be merely a test but must be a comprehensive program. The program must include the provision of understandable information for both patients and providers to ensure informed decision-making, timely access to the screening test, a system of notification of results and referral to follow-up testing, and access to intervention. The screening process must allow patients to decline intervention at each step throughout the process. A screening program must undertake regular
clinical audit to evaluate local performance and should have the flexibility to incorporate new technology.

Appendix A provides a glossary of terms commonly used in screening.

**IMPORTANT CONCEPTS UNDERLYING PRENATAL GENETIC SCREENING**

Multiple marker screening (MMS) uses a combination of maternal age and two or more biochemical tests, with or without an ultrasound examination, to produce a single result for risk of Down syndrome, trisomy 18, and ONTDs, which is used to offer options for clinical management. A screen is positive when one or more of the screened disorders falls above a designated risk cut-off. Counselling and further testing options are offered when a screen is positive. In the discussion of prenatal screening, the terms false positive rate (FPR), or positive rate (PR), and detection rate (DR) are used (see Appendix A). As screening performance improves, the FPR decreases and the DR increases. A risk cut-off might be chosen based upon the desired DR, FPR, or a combination of both. A risk cut-off is expressed as the risk or likelihood of the condition being present in the fetus at term or at mid-trimester. The risk for the latter will be higher because 23% of fetuses with Down syndrome are miscarried between mid-trimester and term.

The other commonly used term in multiple marker screening is multiples of the median (MoM). Each marker result, including both biochemistry and nuchal translucency measurements, can be expressed in MoM. The absolute value of the assayed marker is divided by the gestation specific median value of the marker in the measuring laboratory. This allows for direct comparison of results between laboratories.

**SCREENING FOR CHROMOSOMAL ANOMALIES**

Traditionally, in Canada, the option of invasive testing has been recommended when a woman’s risk of having a pregnancy with a chromosome anomaly was higher than the risks associated with the common invasive procedure (amniocentesis or chorionic villus sampling). New developments in maternal serum and ultrasound screening improved the ability to identify pregnancies at increased risk of Down syndrome, trisomy 18, and other chromosomal abnormalities. This allows use of these screening tests to identify pregnancies at high enough risk to warrant diagnostic testing which has a risk of pregnancy loss.

The most common chromosome conditions associated with advanced maternal age involve the presence of an additional chromosome (21, 18, 13, or X). Only Down syndrome, trisomy 18, and trisomy 13 are associated with congenital anomalies and mental handicap. With ultrasound and maternal serum screening, pregnancies affected by these conditions can now be recognized with a significant degree of reliability. The practice of using solely the previous cut-off of maternal age of 35 or over at the estimated date of delivery (EDD) to identify at-risk pregnancies should
be abandoned. The maternal age-related risk should be modified by additional non-invasive markers, which consist of maternal serum markers and ultrasound assessment.

**CHANGING THE STANDARD OF CARE: SCREENING BY MATERNAL AGE ONLY LIMITED TO WOMEN AGED 40 OR OVER AT ESTIMATED DATE OF DELIVERY**

The probability of conceiving a fetus with a trisomy increases with maternal age. Prenatal screening for chromosome anomalies starts with a discussion of the maternal age-related risk of having a baby with chromosome abnormalities. The simplest of screens involves asking a woman her age. Since the 1970s, if a woman was 35 years or over at the time of delivery, she was considered to be screen positive and was offered amniocentesis or chorionic villus sampling (CVS); if under 35 years, she was screen negative and no further testing was offered. With this approach, if 15% of pregnant women in a given population are ≥ 35 years of age, approximately 40% of cases of Down syndrome will be detected with a 15% false positive rate. Maternal age screening is inferior to newer screening approaches which use multiple biochemical markers with or without a first trimester ultrasound assessment of nuchal translucency. These latter strategies provide a greatly reduced FPR and a substantially improved DR when applied across all age groups. It has been suggested that maternal age alone as a screening strategy should be abandoned. The argument to continue screening on the basis of maternal age alone is that chromosome analysis by invasive testing will detect other aneuploidies related to maternal age, e.g., trisomy 13, 47,XXX and 47,XXY, as well as other chromosomal anomalies unrelated to maternal age. However, trisomy 13 occurs considerably less frequently than Down syndrome and is usually associated with multiple abnormalities frequently detected at a screening ultrasound at 18 to 22 weeks. Sex chromosome abnormalities (47,XXX; 47,XXY) are not screened for by ultrasound or by a maternal serum screen, but the risk of their occurrence approaches 1:200 only for women over 44 years of age. Based on these arguments, screening using maternal age alone should be abandoned except for women over the age of 40. All pregnant women, regardless of age, should be offered a prenatal non-invasive screening test for risk modification of Down syndrome and trisomy 18, and they should be offered invasive testing only if the risk of a chromosomal abnormality is above the risk cut-off set for the screening test. Women over 40 years at EDD also should be counselled regarding non-invasive screening to modify their risk before deciding on CVS/amniocentesis, and they should be informed of the option of invasive testing on the basis age alone.

**Recommendations**

1. All pregnant women in Canada, regardless of age, should be offered through an informed consent process a prenatal screening test for the most common clinically significant fetal aneuploidies in addition to a second trimester ultrasound for dating, growth and anomalies. (I-A)

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**Table 2. Current available screening options and their screening performance**

<table>
<thead>
<tr>
<th>Screening option</th>
<th>Markers</th>
<th>1st /2nd trimester</th>
<th>Term risk cut-off</th>
<th>DR (%)</th>
<th>FPR (%)</th>
<th>OAPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Options that meet the minimum standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTS(^8,13)</td>
<td>NT, free β-hCG, PAPP-A, MA</td>
<td>1st</td>
<td>1 in 325</td>
<td>83</td>
<td>5.0</td>
<td>1:27</td>
</tr>
<tr>
<td>Quad screening(^14)</td>
<td>AFP, uE3, free β-hCG, inhibin A, MA</td>
<td>2nd</td>
<td>1 in 385</td>
<td>77</td>
<td>5.2</td>
<td>1:50</td>
</tr>
<tr>
<td>IPS(^8,13)</td>
<td>NT, PAPP-A, AFP, uE3, free β-hCG/total hCG, inhibin A</td>
<td>1st &amp; 2nd</td>
<td>1 in 200</td>
<td>87</td>
<td>1.9</td>
<td>1:10</td>
</tr>
<tr>
<td>IPS without inhibin A(^5)</td>
<td>NT, PAPP-A, AFP, uE3, total hCG, MA</td>
<td>1st &amp; 2nd</td>
<td>1 in 200</td>
<td>88</td>
<td>3.0</td>
<td>1:20</td>
</tr>
<tr>
<td>Serum IPS(^8,13)</td>
<td>PAPP-A, AFP, uE3, free β-hCG/total hCG, inhibin A</td>
<td>1st &amp; 2nd</td>
<td>1 in 200</td>
<td>85</td>
<td>4.4</td>
<td>1:26</td>
</tr>
<tr>
<td>Options that do not meet the minimum standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age(^3)</td>
<td>MA</td>
<td>1st &amp; 2nd</td>
<td>1 in 385</td>
<td>44</td>
<td>16</td>
<td>1:218</td>
</tr>
<tr>
<td>Triple screening(^3)</td>
<td>AFP, uE3, total hCG, MA</td>
<td>2nd</td>
<td>1 in 385</td>
<td>71</td>
<td>7.2</td>
<td>1:59</td>
</tr>
</tbody>
</table>

DR: Detection rate; FPR: false positive rate; OAPR: Odds of being affected given a positive result; FTS: first trimester combined screening; NT: nuchal translucency; MA: Maternal age; IPS: Integrated prenatal screening.

*Some centres in Canada may offer variation on IPS (sequential screening or contingent screening) with cut-offs set that achieve at least the minimum standard.
2. Maternal age screening is a poor minimum standard for prenatal screening for aneuploidy and should be removed as an indication for invasive testing. Amniocentesis/chorionic villi sampling (CVS) should not be provided without multiple marker screening results except for women over the age of 40. Patients should be counselled accordingly. (I-A)

CHOOSING A SCREEN

The most appropriate screening test for Down syndrome should have the lowest FPR and the highest DR. Cost and logistics should also be considered. Generally, the costs associated with screening are measured by the cost per Down syndrome pregnancy diagnosed. This has been estimated using different screening options in several studies.8–12 One of the difficulties with cost analyses is that the expenses associated with the ultrasound and serum sample analyses vary greatly from one jurisdiction to another. In addition, cost has not been estimated for many screening options, including the second trimester ultrasound. Consequently, a comprehensive cost comparison remains to be undertaken.

Given geographic limitations and resource differences, it is unlikely that a single screening protocol can be endorsed or practically applied for all women across Canada; however, screening options should meet acceptable performance characteristics. At a minimum in 2007, screening should allow for a DR for Down syndrome of 75% with no more than a 5% FPR. By 2008, screening programs should aim to provide a screen that, at a minimum, offers women who present in the first trimester a DR for Down syndrome of 75% with no more than a 3% FPR. Table 2 provides details of currently available screening options and their screening performance. Table 3 details timing of results for options that meet the minimum standard. These include first trimester screening (FTS), quad screening in second trimester, two-step integrated first and second trimester prenatal serum screening with or without nuchal translucency (IPS and serum IPS). IPS can be offered as full integrated screening for all women or as contingent or sequential screening (discussed in detail below). Access to follow-up services should also be ensured. Finally, prenatal screening programs must balance minimizing the FPR (which minimizes the number of invasive procedures needed and thus the number of normal pregnancies lost to CVS or amniocentesis) against the desire to detect as many cases as possible as early in gestation as possible. Some studies suggest that women prefer a lower false positive rate,15–17 but others suggest that women want early diagnosis.18,19 Individual programs should determine what is appropriate for their jurisdiction.

Recommendation

3. In 2007, as a minimum standard, any prenatal screen offered to Canadian women should have a 75% detection rate with no more than a 5% false positive rate for Down syndrome. The performance of the screen should be substantiated by annual audit. (III-B)

REVIEW OF SCREENING OPTIONS

First Trimester Screening: Nuchal Translucency (NT) Combined With Biochemical Markers

Nuchal translucency refers to the subcutaneous layer of fluid behind the fetal neck and lower cranium, which can be visualized on ultrasound. In 1992, Nicolaides et al. described an association between an increased size of the

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Table 3. Available screening options that meet minimum standard

<table>
<thead>
<tr>
<th>Screening methods that meet guideline minimal standard of 75% DR with 5% FPR</th>
<th>Timing of results</th>
<th>Is second trimester US still recommended?</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester screen</td>
<td>1st trimester</td>
<td>Yes</td>
</tr>
<tr>
<td>Second trimester quad screen</td>
<td>2nd trimester</td>
<td>Yes</td>
</tr>
<tr>
<td>Two-step screens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contingent</td>
<td>For most patients, result available in 1st trimester; small proportion of patients require second trimester testing</td>
<td>Yes</td>
</tr>
<tr>
<td>Integrated</td>
<td>Single result in 2nd trimester</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum integrated</td>
<td>Single result in 2nd trimester</td>
<td>Yes</td>
</tr>
<tr>
<td>Sequential</td>
<td>Results in 1st and 2nd trimester for the same patient</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DR: detection rate.
nuchal translucency on the 11 to 14 week fetal ultrasound scan and an increased risk of fetal Down syndrome. Several large studies have shown that NT screening has a DR for Down syndrome ranging from 69% to 75% with an FPR of 5% to 8.1%. In addition, this marker is associated with other numeric chromosome abnormalities as well as other fetal anomalies, such as cardiac defects, diaphragmatic hernia, and a number of single gene disorders, particularly those associated with decreased fetal movement. An NT above the 99th percentile has a sensitivity of 31% and specificity of 98.7% for major congenital heart defects when fetal chromosomes are normal. One in 33 fetuses with an NT above the 95th percentile and 1 in 16 with an NT above the 99th percentile have a major cardiac defect detected. Finding an increased NT at 11 to 14 weeks’ gestation when fetal chromosome patterns are normal warrants offering a detailed ultrasound examination at 18 to 20 weeks, with an assessment of the fetal heart including a four chamber view and view of the outflow tracts as a minimum. In most centres, fetal echocardiograms are recommended.

Two first trimester maternal serum biochemical markers emerged at the same time as NT was being investigated. These are pregnancy-associated plasma protein-A (PAPP-A) and free β-hCG. PAPP-A is lower in Down syndrome pregnancies, and free β-hCG is higher. When a combination of the maternal age-related risk, maternal serum PAPP-A, and free-β-hCG was used, the DR of Down syndrome was 61%, with a 5% false positive rate. The first trimester biochemical markers alone were not as efficacious as second trimester screening; however, a combination of the two first trimester biochemical markers with NT demonstrated a significant improvement over second trimester triple and quadruple screening. First trimester screening (FTS) using maternal age, NT plus PAPP-A, and free-β-hCG will detect 83% of cases of Down syndrome, with a 5% FPR, using a term risk cut-off for Down syndrome of 1:300. It thus fulfills the guideline recommendation.

Limitations on using FTS include the availability and reproducibility of NT as well as the availability of CVS as a diagnostic testing option for those with a screen positive result. Guidelines for measuring NT to maximize reproducibility and accuracy have been developed by the Fetal Medicine Foundation (FMF), UK. The Royal College of Obstetricians and Gynaecologists (UK) study group on first trimester assessment of Down syndrome recommended that NT should be implemented only in centres with appropriately trained sonographers using high-quality equipment and that the results should be subject to regular audit by an external agency. To achieve standardization and maintain quality, the use of NT in a clinical setting requires a program of quality control and maintenance of skills through an ongoing audit of NT measurements (J. Johnson, M. Van den Hof, oral communication, June 2006).

Finally, if local ultrasound services are unable to provide a comprehensive screen for neural tube defects, patients undergoing first trimester screening for aneuploidy should be offered maternal serum alpha fetoprotein (MSAFP) in the second trimester to screen for open neural tube defects.

**Recommendations**

1. First trimester nuchal translucency should be interpreted for risk assessment only when performed by sonographers/sonologists trained and accredited to provide this service and with ongoing quality assurance. (II-2A) It should not be offered as a screen without biochemical markers except in the context of multiple gestation pregnancies. (I-A)

5. For women who undertake first trimester screening (FTS), second trimester serum alpha fetoprotein (AFP) screening and/or ultrasound examination is recommended to screen for open neural tube defect (ONTD). (II-1A)

**Second Trimester Screening**

In the 1970s, alpha fetoprotein was identified as a second trimester marker for open neural tube defects. MSAFP continues to be used as part of multiple marker screening for this purpose but is also effective as a screen for other open fetal defects such as gastroschisis and omphalocele.

In 1983, low MSAFP was noted in a patient who had a baby with trisomy 18. Further investigation showed this marker was low in Down syndrome as well, and for a few years, MSAFP combined with maternal age was used as a marker for Down syndrome. In 1988, Wald et al. demonstrated that the combination of maternal age and MSAFP with two other maternal serum markers, unconjugated estriol (MSuE3) and human chorionic gonadotrophin (MShCG) measured between 15 and 20 weeks’ gestation, would detect 65% of fetuses with Down syndrome with a 5% FPR. These predictions were confirmed in several subsequent studies. Triple marker screening has been available in Canada since 1991. Using a term risk cut-off of 1:385, the triple marker screening detects 72% of fetuses with Down syndrome with a 7% FPR. The triple marker screening also screens for ONTDs, other open fetal defects (e.g., gastroschisis, omphalocele), placental dysfunction, Smith-Lemli-Opitz syndrome, and trisomy 18. The triple screen does not fulfill the guideline’s recommendation. However, DIA (dimeric inhibin-A) is a potential fourth marker that can be added in the second trimester, resulting in the quad screen. Although a relatively weak marker alone, DIA will increase the DR of Down syndrome by 10%,

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**Financial Disclosures and Conflicts of Interest**

This review does not reflect the views of the College of Obstetricians and Gynecologists of Canada (COGC). The COGC played no role in the writing of this article. The COGC does not endorse or recommend any product or service, but the content of this article is consistent with the COGC’s best practice guidelines. The COGC is a registered charity and is dedicated to the improving the health and well-being of women and newborns. The COGC is the voice of women’s health in Canada by promoting best practice guidelines and standards of care in women’s health and obstetrics/gynecology. The COGC is a professional organization representing the spectrum of obstetricians and gynecologists in Canada. The COGC is a professional organization representing the spectrum of obstetricians and gynecologists in Canada.
The risk cut-off can be varied to partially decrease the FPR while increasing the DR by somewhat less than 10%. With a risk cut-off of 1:230 at term, the DR is 75% to 80%, and the FPR is lowered to 3% to 5%, thus meeting the minimal standard set by this guideline.8,13

**Combined First and Second Trimester Options**

**Integrated prenatal screening**

In an effort to further improve performance, the first and second trimester screening tests have been combined into a process called integrated prenatal screening (IPS). Wald et al. predicted that integrating first and second trimester screening would result in an 83% DR for Down syndrome, with a 2.1% FPR at a term risk cut-off of 1:200. IPS was based on the use of PAPP-A and NT in the first trimester and the quad screen in the second trimester with results released when all the testing was completed.34 This approach has been controversial, as the accompanying editorial suggested women had the right to know their results early and that it was unethical to withhold the first trimester results.35 However, when IPS includes a quad screen in the second trimester, studies have shown a detection rate of 85% to 87% with an FPR of 0.8% to 1.5%.8,13 When DIA is excluded from the IPS, the FPR increases to ~2.5% when the first trimester markers are performed at 12 weeks. Full integrated screening meets the guideline minimal standard. The benefit of IPS over FTS is the achievement of a lower FPR and reduction of the number of invasive diagnostic procedures needed.

The optimal time for the PAPP-A measurement is 9 to 10 weeks’ gestation, and the performance of PAPP-A screen decreases between 10 and 13 weeks. The proportion of pregnancies in which a satisfactory NT measurement can be obtained is the highest at 11 to 13 weeks’ gestation. First trimester measurements are usually carried out between 11 and 14 weeks’ gestation as a compromise to make the timing favourable for NT and for PAPP-A.8 IPS also screens for open fetal neural tube defects and trisomy 18.

**Serum integrated prenatal screening**

When NT screening is not available, IPS still can be offered, using PAPP-A tests in the first trimester and triple or quad screening in the second trimester. This approach has an 83% DR for a 4% FPR.8 Alternatively, PAPP-A and free ß-hCG tests can be offered in the first trimester followed by AFP and ßE3 in the second with virtually the same performance. The FPR is 4.2% if PAPP-A is measured at 10 completed weeks, and the FPR is doubled (8.5%) if it is measured at 13 completed weeks.8 In the First- and Second-Trimester Evaluation of Risk (FASTER) trial, serum IPS showed a 4.4% FPR for an 85% DR.13 Serum IPS is a practical option for areas of Canada where there is limited or no access to NT screening.

Given that timing is critical for serum analysis, accurate dating of the pregnancy is very important. Ultrasound dating should be considered if menstrual or conception dating is unreliable.

**Recommendation**

6. First trimester screening (FTS), the first step of integrated screening (with or without nuchal translucency), contingent, and sequential screening are performed in an early and relatively narrow time window. Timely referral is critical to ensure women are able to undergo the type of screening test they have chosen. (II-1A)

**Contingent screening**

The concept of contingent screening has been suggested by Wright et al.36 as an alternative to IPS. In contingent screening, the majority of women receive their result after FTS. Women at high risk (for example, risk > 1/50) are offered invasive testing, and women at low risk (for example, risk < 1/1000) require no further testing. A proportion of women with a risk between two cut-offs (e.g., 1/50 and 1/1000) will go on to have second trimester screening and will receive a combined result. Benn et al. reported the expected screening performance of the contingent strategy by modelling on different risk cut-offs and maternal age distributions of the UK and the US. Performance of contingent screening was comparable with IPS if total hCG/free ß-hCG was measured in both trimesters.37 It is possible to select risk cut-offs that achieve performances similar to IPS, thus meeting the guideline recommendation, while achieving detection of a significant proportion of abnormal pregnancies by the end of the first trimester.38,39 However, in contingent screening, a proportion of women are identified as having an intermediate risk and asked to have the second trimester serum to modify their risk. This result is likely to raise anxiety for these women, who might wish to have invasive testing immediately, thus increasing the FPR.39,40

**Sequential Screening**

Sequential screening selects women for second trimester testing on the basis of their first trimester screening results. Women who receive screen positive FTS results are offered invasive testing. Those with a screen negative result are offered additional serum screening in the second trimester. The removal of screen positive affected cases in the first trimester will decrease the prevalence of Down syndrome in the second trimester and, consequently, lowers the positive predictive value of second trimester serum screening.41,42 As a result the overall cut-off is adjusted to take this in consideration. With appropriate cut-offs, sequential screening has been shown to perform equivalently to full integrated and
contingent screening and meets the guideline recommendations.33,39

Sequential screening that does not incorporate the results of the first trimester testing into the second trimester risk analysis is associated with a significant increased FPR.8,9 Given this high FPR, sequential screening should not be offered unless the second trimester risk incorporates the first trimester results.

Repetitive measures screening
In Down syndrome screening, the choice of markers has been influenced by the extent to which they provide independent information on risk estimation. In 2005, Wright and Bradbury described a mathematical model showing the potential value of screening for Down syndrome using highly correlated repeated measures of serum markers, some of which individually may have poor discriminatory power.43 They postulated that using first trimester NT and repeated measures of uE3 and PAPP-A in the first and second trimester, 85% of Down syndrome can be detected for with an encouragingly low FPR (0.3%), which is a substantial improvement over the IPS. A recent case-control study in a Canadian population has substantiated the mathematical model.44 More recently, Wald et al. demonstrated that the performance of integrated screening is improved when ratios of the levels of the same serum markers measured in both trimesters are used in the risk assessment.45 Although further studies are needed, the reports to date suggest that integrated screening with repeat measurements has the potential to significantly reduce the FPR.

POTENTIAL OF SCREENING OPTIONS TO DETECT CHROMOSOMAL ANOMALIES OTHER THAN DOWN SYNDROME AND OTHER GENETIC CONDITIONS

In pregnancies with trisomy 18, first trimester PAPP-A is decreased, NT is enlarged, and second trimester serum levels of AFP, uE3, hCG, and inhibin-A are significantly reduced.46–49 Many centres are now routinely screening for trisomy 18 using protocols designed for this anomaly. With second trimester triple marker screening, at a risk cut-off of ≥1: 100, 60% of trisomy 18 pregnancies can be detected for with a DR of 62% for a FPR of 0.33%.67 However, the screen is not specific for SLOS since it detects a number of rare disorders of cholesterol and estriol biosynthesis, such as congenital adrenal hypoplasia and Zellweger syndrome, as well as a relatively common and mild disorder, X-linked steroid sulfatase deficiency (X-linked ichthyosis).68

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder associated with mental retardation and multiple congenital anomalies. The minimum incidence is estimated to be 1 in 60 000.63 SLOS is due to an abnormality in cholesterol synthesis resulting in a low cholesterol concentration and accumulation of its precursors in blood and tissue.64 SLOS can be diagnosed prenatally by an abnormally elevated amniotic fluid 7-dehydrocholesterol concentrations.65 In pregnancies with SLOS, maternal serum uE3 as well as AFP and hCG are reduced.66 A screening protocol has been developed for this syndrome that provides a DR of 62% for a FPR of 0.33%.67 Although the screen is not specific for SLOS since it detects a number of rare disorders of cholesterol and estriol biosynthesis, such as congenital adrenal hypoplasia and Zellweger syndrome, as well as a relatively common and mild disorder, X-linked steroid sulfatase deficiency (X-linked ichthyosis).68

THE USE OF ULTRASOUND IN SCREENING FOR CHROMOSOMAL ANOMALIES

At 18 to 20 weeks’ gestation, all women should be offered a screening ultrasound that meets previously established minimum standards.69 Most major fetal anatomic abnormalities should be detected with this screen. In particular, the majority of open neural tube defects should be detected by ultrasound.70 Ultrasound can also detect “soft markers,” which are features that increase the a priori risk of fetal aneuploidy but also can be variations of normal. When used alone, second trimester ultrasound soft markers do not effectively discriminate between unaffected fetuses and fetuses with Down syndrome, because of the high positive rate from the large number of potential markers.71–74 Ultrasound soft markers have been comprehensively reviewed by Van den Hof et al.75 Both soft markers and anomalies identified in the 18- to 20-week ultrasound can be used to modify any risk established by age or prior screening. In the absence of soft markers and anomalies, a reduction of risk can be assumed; however, this should only be done in an established centre performing tertiary level scans. In this circumstance, a negative likelihood ratio of 0.5 is often used unless centre-specific levels are determined through clinical audit.

Ultrasound screening for delayed ossification of the fetal nasal bone can be done in the first or second trimester. The first trimester ultrasound that determines the presence or absence of the nasal bone between 11 and 14 weeks of
gestation may be more likely to be incorporated into other screening modalities. First trimester assessment of the fetal nasal bone was described by Cicero et al. and detected 77% of Down syndrome cases. Subsequent work has shown that there is a DR of 68.8% and that the FPR depends upon maternal ethnicity (9% in Afro-Caribbeans, 5% in Asians, and 2.2% in Caucasians). The FPR also varied with crown–rump length (increasing with decreasing crown–rump length) and NT (increasing with increasing NT). The difficulty in performing first trimester nasal bone sonography consistently in the general population might limit the usefulness of this screening technique. A study of intra- and inter-operator variability in fetal nasal bone assessment during the first trimester showed that the assessment was only fairly reproducible. Therefore, training and quality assurance programs must be developed before nasal bone assessment as an additional screening technique can be implemented in the general population.

**Recommendation**

7. Soft markers or anomalies in the 18- to 20-week ultrasound can be used to modify the a priori risk of aneuploidy established by age or prior screening provided the scan is undertaken in an established centre performing tertiary level ultrasound. In the absence of ultrasound soft markers or anomalies, a negative likelihood ratio of 0.5 should be used. Evaluation of the fetal nasal bone in the first trimester remains technically difficult and should not be incorporated as a screen until locally established as an effective risk assessment tool. (III-D)

**SPECIAL CONSIDERATIONS FOR MULTIPLE GESTATION PREGNANCIES**

Down syndrome risk adjustment in twins or multiple pregnancies is complicated since it poses complex practical and ethical issues. Because of the absence of data on screening markers in affected twin pregnancies, maternal serum screening usually is not undertaken, and screening relies on maternal age and ultrasound findings.

The use of an individual fetal NT allows the calculation of specific risks for each fetus and, therefore, can identify a fetus or fetuses at increased risk. Using maternal age in specific risks for each fetus and, therefore, can identify a

**FACTORS POTENTIALLY AFFECTING SCREENING PERFORMANCE**

Appendix B provides details of factors that may affect screening performance. These include accuracy of gestational dating, maternal weight, ethnicity, insulin dependant diabetes mellitus, accuracy of NT and serum marker measurements, and the use of assisted reproduction technologies.

**GENERAL CONSIDERATIONS**

Screening practice differs across Canada and will also change over time. By 2008, screening programs should aim to provide a screen that, as a minimum, offers women who present in first trimester a DR for Down syndrome of 75% with no more than a 3% FPR. Practitioners should stay updated on the screening modalities available in their area. To facilitate this process, Appendix C lists contact numbers for all of the provinces.

**Recommendations**

8. Health care providers should be aware of the screening modalities available in their province or territory. (III-B)

9. Screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding to adjust the program to new technology and protocols. (II-3B)

10. Screening programs should show respect for the needs and quality of life of persons with disabilities. Counselling should be nondirective and should respect a woman’s choice to accept or to refuse any or all of the testing or options offered at any point in the process. (III-I)

11. By 2008, screening programs should aim to provide a screen that, as a minimum, offers women who present in first trimester a detection rate of 75% for Down syndrome, with no more than a 3% false positive rate. (III-B)

**REFERENCES**


4. Resta RG. Changing demographics of advanced maternal age (AMA) and the impact on the predicted incidence of Down syndrome in the United


21. Mulvey S, Zachariah R, McIlwaine K, Wallace EM. Do women prefer to have screening tests for Down syndrome that have the lowest screen-positive rate or the highest detection rate? Prenat Diagn 2003;23:828–32.


APPENDIX A. SCREENING TERMINOLOGY

Affected individuals: Individuals who have the disorder for which the screen is being performed.

Cut-off level: The value of a test variable that distinguishes screen positive from screen negative results. The screening cut-off will affect both the detection and false positive rates—the higher the cut-off, the lower the false positive rate and the lower the detection rate.

Detection rate (DR) or sensitivity: The proportion of affected individuals with positive screening results (usually expressed as a percentage).

False positive rate (FPR): The proportion of unaffected individuals with positive screening results (usually expressed as a percentage). It is the complement of the specificity.

Incidence: The number of new cases of a disorder that arise during a specific period of time, such as a year. This is usually expressed as a rate per 1000.

Likelihood ratio (LR): The likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that that same result would be expected in a patient without the target disorder. The likelihood ratio for a population is the detection rate divided by the false positive rate.

Multiple of the Median (MoM): The observed value of a specific marker divided by the median value for that marker in a specified population (in prenatal screening, usually pregnancies of the same gestational age).

Marker: A biological measurement that when present at an abnormal level may indicate the presence of disease.

Negative Predictive Value: The number of unaffected individuals with negative results (true negatives) divided by the total number of individuals with a negative result, both affected and unaffected.

Odds of being affected given a positive result (OAPR): The ratio of the number of affected individuals with positive test result to the number of unaffected individuals with positive result.

Positive predictive value (PPV): The number of affected individuals with positive results (true positives) divided by the total number of individuals with positive result, both affected and unaffected. It is the odds of being affected given a positive result expressed as a proportion or percentage.

Positive rate: The sum of true and false positives. For most screens, the positive rate is virtually equal to the false positive rate but as the FPR decreases, this becomes a less reliable approximation. The screen positive rate is a useful parameter for the estimation of resource requirements for follow-up services.

Prevalence: The number of cases of a disorder present at a point in time or during a specified period. This is usually expressed as a rate per 1000.

Quality assurance: The policy, procedures, and systematic actions established in an enterprise for the purpose of providing and maintaining a specified degree of confidence of a screening test.

Receiver operator curve (ROC): It is a plot of the true positive rate against the false positive rate for the different possible cut points of a test. An ROC curve demonstrates the trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity). Accuracy of the test is measured by the area under the ROC curve.

Specificity: The proportion of unaffected individuals with negative result.

Unaffected individuals: Individuals who do not have the disorder for which the screen is being performed.

APPENDIX B. FACTORS POTENTIALLY AFFECTING SCREENING PERFORMANCE

Gestational dating methods
Accurate dating is important. Ultrasound improves the precision of gestational age estimation, and hence reduces the standard deviation of each screening marker. This effect is greater for markers whose concentrations change most with gestational age. For all marker combinations, the FPR is lower by about 2% when gestational age is estimated using diagnostic imaging. For example, for a DR of 85%, scan dating could reduce the FPR of serum IPS from 4.2% to 2.7%.8

Maternal weight
There is a negative association between the levels of maternal serum markers and maternal weight which is due to the dilution effect produced by the physiologic increase in blood volume.84 The trend with first trimester markers is similar to that seen with second trimester markers.85 With second trimester screening, maternal weight adjustment increases DR by about 1% for a given FPR, or reduces FPR by 0.2% for a given DR.14 Weight adjustment is beneficial if there is a marginally elevated AFP when screening for
ONTD. When interpreting measurements of serum markers, many screening centres routinely adjust for maternal weight. It has been suggested that published weight correction formulae may not be optimal because of differences in mean weight between the population served and the populations used to derive the formulae. Each laboratory should calculate its own weight adjustment formulae.

Weight adjustment does not appear to be necessary for NT risk adjustment because it increases only by a clinically insignificant amount with increasing maternal weight.

Ethnic origin

There are differences in the levels of screening markers between women of different ethnic origins after accounting for maternal weight. Compared with Caucasian women, Black women have maternal serum AFP that is 15% higher, total hCG that is 18% higher, PAPP-A that is 35% higher, and inhibin A that is 8% lower. Compared with Caucasian women, South Asian women have AFP that is 6% lower, uE3 that is 7% higher, total hCG that is 6% higher, and PAPP-A that is 17% higher. Higher levels of first trimester PAPP-A and ß-hCG are seen in Asian women, and higher uE3 is seen in Aboriginal women.

Statistically significant differences in NT measurement have been found between ethnic groups. However, it seems these differences may be too small to warrant correction.

Insulin-dependent diabetes mellitus

Some second trimester serum markers tend to be lower in women with insulin dependent diabetes mellitus. After weight correction, AFP is ~10% lower and uE3 is ~5% lower in diabetic women. No change in other markers in diabetic women has been demonstrated. To allow for the difference, the observed MoM for a woman with diabetes is divided by the corresponding median MoM in diabetic women without Down syndrome pregnancies. Because of the lack of data in diabetic women who have a Down syndrome pregnancy, a “pseudo risk” can be calculated for diabetic women.

It appears that NT measurement, free ß-hCG, and PAPP-A in women with and without insulin dependent diabetes are not significantly different.

Measurement of serum screening markers

Guidelines for measuring serum markers have been established (NCCLS document 1/LA25-A, 2005). To achieve standardization and maintain quality, the use of serum markers in a clinical setting requires a program of quality control and maintenance of skills through an ongoing external audit of serum measurements.

Measurement of NT

Guidelines for measuring NT to maximize reproducibility and accuracy have been described above.

Assisted reproduction

When a pregnancy is a result of in vitro fertilization (IVF), the maternal age used for the determination of the risk of Down syndrome is the age of the donor at the time the egg was harvested.

Data from most published studies show second trimester serum levels of hCG and ß-hCG are higher and uE3 is lower in pregnancies conceived through IVF. There were no significant differences in the levels of AFP and inhibin A between IVF and non-IVF pregnancies. The variation in hCG is said to be driven by the continuing high progesterone concentrations following hormonal treatment. Because of the higher hCG and lower uE3 levels, the FPR of second trimester screening is nearly doubled in IVF pregnancies. However, results from a recent study in France based on ~1000 IVF pregnancies found no differences in the values of maternal serum AFP, uE3, and hCG between IVF pregnancies and controls. The FPR was similar in the two groups. Wald et al., 1999, suggested that adjustments for IVF pregnancies could avoid this high FPR. However, results from a recent study in France based on ~1000 IVF pregnancies found no differences in the values of maternal serum AFP, uE3, and hCG between IVF pregnancies and controls. The FPR was similar in the two groups.

In the first trimester, a lower value of PAPP-A has been reported in IVF pregnancies, but data on NT and first trimester free ß-hCG remain inconsistent. Many screening programs routinely collect information on IVF; however, whether adjustment is necessary needs further investigation.
## Appendix C. List of screening centres and clinics across Canada

<table>
<thead>
<tr>
<th>Province and area</th>
<th>Department/hospital</th>
<th>Address</th>
<th>Contact number</th>
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<tbody>
<tr>
<td><strong>Newfoundland</strong></td>
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</tr>
<tr>
<td>St. John’s</td>
<td>Provincial Medical Genetics Program</td>
<td>Health Sciences Centre, 300 Prince Philip Drive, St John’s NL A1B 3V6</td>
<td>(709) 777 4363</td>
</tr>
<tr>
<td>Nova Scotia, New Brunswick and Prince Edward Island</td>
<td>Maritime Prenatal Screening and Diagnosis</td>
<td>IWK Health Center, 5850–5980 University Ave, PO Box 9700 Halifax NS B3K 6R8</td>
<td>(902) 470 8321</td>
</tr>
<tr>
<td><strong>Quebec</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montreal</td>
<td>Centre de Diagnostic Prénatal</td>
<td>CHU Sainte-Justine 3175 Côte-Ste-Catherine Montréal, Québec H3T 1C5</td>
<td>(514) 345 7737</td>
</tr>
<tr>
<td>Quebec</td>
<td>Service de biochimie médicale</td>
<td>CHU de Québec (Hôpital St-François-d’Assise) 10 rue de l’Espinay, G1L 3L5</td>
<td>(418) 525 4444 ext. 53576</td>
</tr>
<tr>
<td>Sherbrooke</td>
<td>Clinique de médecine foeto-maternelle</td>
<td>CHU de Sherbrooke – Fleurimont 3001, 12 ème avenue nord J1H 5N4</td>
<td>(819) 346 1110 ext. 14726</td>
</tr>
<tr>
<td><strong>Ontario</strong></td>
<td></td>
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</tr>
<tr>
<td>Hamilton</td>
<td>Regional Prenatal Diagnosis Services, Hamilton Health Sciences</td>
<td>1200 Main Street, Hamilton ON L8N 3Z5</td>
<td>(905) 521 2100 ext. 72647</td>
</tr>
<tr>
<td>Kingston</td>
<td>Medical Genetics Unit, Kingston General Hospital</td>
<td>20 Barrie Street, Kingston ON K7L 3J6</td>
<td>(613) 533 6310</td>
</tr>
<tr>
<td>London</td>
<td>Medical Genetics Program of S.W. Ontario</td>
<td>London Health Sciences Centre, 800 Commissioners Road East, London ON N6A 5W9</td>
<td>(519) 685 8140</td>
</tr>
<tr>
<td>Mississauga</td>
<td>Genetics Clinic, Credit Valley Hospital</td>
<td>2200 Eglinton Ave West, Mississauga, ON L5M 2N1</td>
<td>(905) 813 4104</td>
</tr>
<tr>
<td>North Bay</td>
<td>North Bay Parry Sound District Health Unit, Genetics Program</td>
<td>681 Commercial Street, North Bay ON P1B 4E7</td>
<td>(705) 474 1400</td>
</tr>
<tr>
<td>North York</td>
<td>Maternal Serum Screening Program, Dept. of Genetics, North York General Hospital</td>
<td>4001 Leslie Street, 3rd floor, SE Wing, Toronto ON M2K 1E1</td>
<td>(416) 756 6055</td>
</tr>
<tr>
<td>Orillia</td>
<td>Simcoe County Genetics Services, Orillia Soldiers’ Memorial Hospital</td>
<td>170 Colborne Street West, Orillia ON L3V 2Z3</td>
<td>(705) 327 9154</td>
</tr>
<tr>
<td>Oshawa</td>
<td>Clinical Genetics Lakeridge Health Oshawa</td>
<td>1 Hospital Court, Oshawa ON I1G 2B9</td>
<td>(905) 433 2733</td>
</tr>
<tr>
<td>Ottawa</td>
<td>Eastern Ontario Regional Genetics Program, Children’s Hospital of Eastern Ontario</td>
<td>401 Smyth Road, Ottawa ON K1H 8L1</td>
<td>(613) 737 7600 ext. 2138</td>
</tr>
<tr>
<td>Peterborough</td>
<td>Genetics Program, Peterborough County City Health Unit,</td>
<td>10 Hospital Drive, Peterborough ON K9J 8M1</td>
<td>(705) 743 1000</td>
</tr>
<tr>
<td>Sault Ste. Marie</td>
<td>Algoma Counselling Services Algoma Health Unit</td>
<td>63 East Street, Unit 1, Sault Ste-Marie ON P6A 3C4</td>
<td>(705) 541 7057</td>
</tr>
<tr>
<td>Scarborough</td>
<td>Rouge Valley Health System-Centenary Site, Genetics Clinic</td>
<td>2867 Ellesmere Road, Scarborough ON M1E 4B9</td>
<td>(416) 281 7425</td>
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<tr>
<td>Sudbury</td>
<td>Sudbury Regional Hospital, Genetics Counselling Services</td>
<td>41 Ramsey Lake Road, Sudbury ON P3E 5J1</td>
<td>(705) 675 4786</td>
</tr>
<tr>
<td>Thunder Bay</td>
<td>Northwestern Ontario Regional Genetics Program, Thunder Bay District Health Unit</td>
<td>999 Balmoral Street, Thunder Bay ON P7B 6E7</td>
<td>(807) 625 5924</td>
</tr>
<tr>
<td>Timmins</td>
<td>Porcupine Health Unit</td>
<td>169 Pine Street South, Timmins ON P4N 8B7</td>
<td>(705) 261 1181</td>
</tr>
<tr>
<td>Toronto</td>
<td>Prenatal Diagnosis Program, Mt. Sinai Hospital</td>
<td>700 University Avenue-Hydro Building, Toronto ON M5G 1Z5</td>
<td>(416) 586 4946</td>
</tr>
<tr>
<td>Windsor</td>
<td>Windsor-Essex County Health Unit, Genetics Services</td>
<td>1005 Ouellette Avenue, Windsor ON N9A 4J8</td>
<td>(519) 258 2146</td>
</tr>
<tr>
<td>York</td>
<td>Genetics Clinic, York Central Hospital</td>
<td>10 Trench Street, Richmond Hill ON L4C 4Z3</td>
<td>(905) 883 1212 ext. 7579</td>
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## Appendix C. continued

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<thead>
<tr>
<th>Province and area</th>
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<td><strong>Manitoba</strong></td>
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<tr>
<td>Winnipeg</td>
<td>Program in Genetics and Metabolism Health Sciences Center</td>
<td>FE 229, 840 Sherbrook Street Winnipeg MB R3A 1R9</td>
<td>(204) 787 4804</td>
</tr>
<tr>
<td><strong>Saskatchewan</strong></td>
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</tr>
<tr>
<td>Regina</td>
<td>Regina General Hospital</td>
<td>1440 - 14th Avenue, Regina SK S4P OW5</td>
<td>(306) 766 4157</td>
</tr>
<tr>
<td>Saskatoon</td>
<td>MSS Northern Saskatchewan</td>
<td>300 - 149 Pacific Avenue, Saskatoon SK S7K 1N8</td>
<td>(306) 653 5970</td>
</tr>
<tr>
<td><strong>Alberta</strong></td>
<td></td>
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</tr>
<tr>
<td>Calgary Health Region</td>
<td>Southern Alberta Centre for Maternal Fetal Medicine</td>
<td>Suite 100 - 3280 Hospital Drive NW Calgary AB T2N 4N1</td>
<td>(403) 289 9269</td>
</tr>
<tr>
<td>Capital Health Region</td>
<td>Edmonton Early Pregnancy Risk Assessment Program Perinatal Clinic, Royal Alexandra Hospital</td>
<td>10240 Kingsway Ave, Edmonton AB T5H 3V9</td>
<td>(780) 735 4813</td>
</tr>
<tr>
<td><strong>British Columbia</strong></td>
<td>Provincial Prenatal Genetic Screening Program</td>
<td>4500 Oak Street, Vancouver BC V6H 3N1</td>
<td>(604) 875 2157</td>
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</table>