Counselling Considerations for Prenatal Genetic Screening

INTRODUCTION

Trisomies 21, 18, and 13 are the most frequently occurring fetal aneuploidies, although all have been observed at term. Eighty percent of fetuses with trisomy 18 or 13 and 30% with trisomy 21 die in utero between 12 and 40 weeks of gestation.

Trisomy 21, or Down syndrome, is the most common viable chromosomal anomaly, with an incidence of 1/770 live births. Individuals with trisomy 21 may have physical abnormalities such as a cardiac defect, early onset Alzheimer disease, and/or increased rates of leukemia, and all will have some degree of developmental delay. The 18- to 20-week ultrasound examination will show no abnormal findings in 50% of fetuses with trisomy 21.

The risk of having an affected fetus increases with maternal age. However, as most pregnancies occur in young women, most fetuses with trisomy 21 occur in younger mothers.

SCREENING

Prenatal screening for fetal aneuploidy is a rapidly changing field, and there are variations in screening protocols both provincially and regionally. Clinicians should be aware of the availability of and protocols for screening in their geographical area.

Biochemical and ultrasound screening tests are now available during pregnancy to assess the risk of having a fetus with trisomy 21. If the risk of trisomy 21 is higher than a specified risk cut-off as determined by the screening program, a diagnostic test (e.g., amniocentesis) is offered to confirm or exclude the presence of trisomy 21 (and some other chromosome abnormalities).
It is important to ensure that these screening tests are offered within the context of an organized program, ensuring laboratory tests and ultrasound operators have appropriate validation to meet quality assurance standards.

Screening is intended to identify women in the general pregnancy population who are at increased risk of having a child with an anomaly. Health care professionals should discuss the screening tests with all pregnant women. Information pamphlets can also be helpful in explaining the purpose and limitations of screening tests, but health care providers should be aware that some women may not have sufficient English or French to understand them. Health care providers must be satisfied that patients understand the screening available and that screening is entirely voluntary, and that they are making an informed decision about whether to have testing. The decision should be documented.

**Screening Methods**

Screening can be divided into two broad categories:

1. Maternal serum sampling: measure of maternal biochemical markers in the first and/or second trimester of pregnancy. This can be done with or without ultrasound screening.

2. Ultrasound screening: measure of first trimester nuchal translucency and other ultrasound markers in the first and/or second trimester of pregnancy.

Their performance, in terms of sensitivity and specificity, varies according to the approach, but the results are improved by using a combination of these methods. For example, an ultrasound examination is performed in the first trimester, and blood tests in the first and second trimester to provide a single assessment of risk. It is not appropriate to use one method to assess risk and then use another method to give a separate risk assessment. When multiple screening options are available, factors to consider include the detection rate and false-positive rate of the screening test, and the gestational age at the time testing is considered.

**Screen Positive Rate**

- This is the proportion of the screened population who test positive. It includes both true positives and false positives. Women who screen positive are eligible for and are offered counselling and invasive testing. Most women who screen positive will not have a fetus with trisomy 21; that is, they will have a false-positive result.

**Sensitivity (Detection Rate)**

- Sensitivity refers to the test’s ability to detect all individuals who have the condition.

- The higher the sensitivity of the screening test, the more likely it is to identify individuals with the condition.

- Sensitivity is the probability that an individual who has the condition will test positive; it is not the risk for trisomy 21 after a positive screening test result.

**Specificity**

- Specificity refers to the probability that an individual who does not have the condition will test negative.

- The higher the specificity of the screening test, the more likely it is to correctly identify individuals who do not have the condition.

- Specificity measures the test’s ability to identify only individuals who have the condition.

**Positive Predictive Value**

- Positive predictive value is the probability that an individual has the condition given a positive screening result.

- Positive predictive value is determined/assessed on the basis of test sensitivity and specificity, and the prevalence of the condition.

**Negative Predictive Value**

- Negative predictive value is the probability that an individual does not have the condition given a negative screening result.

**TIPS FOR PRE-SCREENING COUNSELLING**

- Counsel your patient that all pregnant women have some risk of having a fetus affected by trisomy 21, 18, or 13.

- Tell your patient that prenatal screening will use specific maternal and pregnancy factors (e.g., age, ethnicity) to assess her individual risk of having an affected fetus.

- Discuss the following points with your patient.
  - Maternal age is one factor used in the assessment of risk, and the screening result is more likely to be positive with increasing age.
  - A positive screening result may provide an older woman with a risk assessment/adjustment lower than the risk associated with her age alone.
  - The screening may assess a younger woman’s risk as greater than that indicated by her age alone, but it may not be high enough to result in a positive screening test result.
Counselling Considerations for Prenatal Genetic Screening

Current available screening options and their screening performance*

<table>
<thead>
<tr>
<th>Screening option</th>
<th>Markers</th>
<th>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>FTS¹,²</td>
<td>NT, free β-hCG, PAPP-A, MA</td>
<td>First</td>
<td>1 in 325</td>
<td>83</td>
<td>5.0</td>
<td>1.27</td>
</tr>
<tr>
<td>Quad screening³</td>
<td>AFP, uE3, free β-hCG, inhibin A, MA</td>
<td>Second</td>
<td>1 in 385</td>
<td>77</td>
<td>5.2</td>
<td>1.50</td>
</tr>
<tr>
<td>IPS¹,²</td>
<td>NT, PAPP-A, AFP, uE3, free β-hCG/total hCG, inhibin A, MA</td>
<td>First and second</td>
<td>1 in 200</td>
<td>87</td>
<td>1.9</td>
<td>1.10</td>
</tr>
<tr>
<td>IPS without inhibin A¹</td>
<td>NT, PAPP-A, AFP, uE3, total hCG, MA</td>
<td>First and second</td>
<td>1 in 200</td>
<td>88</td>
<td>3.0</td>
<td>1.20</td>
</tr>
<tr>
<td>Serum IPS¹,²</td>
<td>PAPP-A, AFP, uE3, free β-hCG/total hCG, inhibin A</td>
<td>First and second</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 age⁴</td>
<td>MA</td>
<td>First and second</td>
<td>1 in 385</td>
<td>44</td>
<td>16</td>
<td>2.18</td>
</tr>
<tr>
<td>Triple screening⁴</td>
<td>AFP, uE3, total hCG, MA</td>
<td>Second</td>
<td>1 in 385</td>
<td>71</td>
<td>7.2</td>
<td>1.59</td>
</tr>
</tbody>
</table>

*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.

| DR: detection rate; FPR: false positive rate; OAPR: odds of an affected pregnancy result; FTS: first trimester combined screening; NT: nuchal translucency; hCG: human chorionic gonadotropin; PAPP-A: pregnancy associated plasma protein A; MA: maternal age; IPS: integrated prenatal screening; AFP: alpha fetaprotein; uE3: unconjugated estriol. |


- Counsel your patient that a positive screen will mean that her risk is above a pre-determined cut-off (set by regional programs), not that her fetus is necessarily affected. Some patients may have difficulty understanding the difference between a screening test and a diagnostic test.
- Counsel your patient that her risk is specific and personalized. For example, a risk of 1:100 means that for one woman carrying an affected fetus, there are 99 women carrying a fetus that is not affected. Prenatal aneuploidy screening using age and nuchal translucency measurement in the first trimester is appropriate for screening in multiple gestations. For multiple gestations, it is important to check with the screening centre close to you, as availability of maternal serum screening varies from centre to centre.
- When screening is offered, discuss options and the invasive prenatal testing that may need to be considered after screening.
- Tell your patient that if screening is negative, no further testing is indicated other than routine second trimester ultrasound. Remind her that there is a risk to invasive procedures. Inform the patient that negative screening does not guarantee the birth of a healthy baby and that her child could still be born with an aneuploidy or another genetic or developmental condition not detected through screening. Inform your patient that if the screening test is positive she is eligible for diagnostic testing.
  - This testing would be done by amniocentesis, which carries a procedural risk of 1/100 to 1/175 for loss of the pregnancy or by chorionic villus sampling, which carries a procedural risk of 1/100 for loss of the pregnancy.²³
  - Ensure your patient is aware that diagnostic testing is entirely voluntary.
  - Ensure your patient knows that she has the option of continuing or terminating the pregnancy if the test shows that her fetus has an aneuploidy or another significant chromosomal anomaly. It is a common misconception that screening is offered only to patients who would terminate a pregnancy if an anomaly were found. It is important to tell patients who may choose to continue the pregnancy that their fetus will be given the best care possible. In the case of chromosomal anomalies that have an extremely poor prognosis, this may include referring the patient to a neonatologist to discuss palliative...
care. For the care of a fetus with Down syndrome this should include

- Ensuring that the fetus receives necessary testing and monitoring, such as fetal echocardiogram and increased surveillance.

- Informing the patient of the support available for parents choosing to raise a child with Down syndrome, including the Canadian Down Syndrome Society.

  - Be aware that undecided patients may pursue or decline screening and testing at any point in the screening process.

**POST-SCREENING COUNSELLING**

A screening program should include a reliable laboratory that can provide a report of results within a working week. Screening results should be reported to the patient as soon as possible after results have been reported to the practitioner. Ideally, screening results should be discussed in person.

**Negative Screen**

For women with a negative screen, as defined by a predetermined cut-off, counselling should include the risk for trisomy 21 determined by screening rather than by pre-screening risk determined by age. As part of counselling, the patient should be informed that a negative screen does not guarantee that her fetus does not have one of the conditions screened for; however, the risk is low enough that invasive testing will not offered. Routine second trimester ultrasound will still be carried out. In younger women, the assessment may indicate that their risk is greater than the risk that would have been determined by age alone but may result in a negative screen. Counselling may be needed to help some women understand that although the risk is increased, the result is still negative, and invasive diagnostic testing is not required.

As regions differ with respect to the use of ultrasound markers, regional protocols will guide any further adjustment of risk. If one or more ultrasound markers are present at the time of the anatomical survey, the risk for trisomy 21, as determined by screening, will be adjusted by the likelihood ratio assigned to the specific marker(s).

The risk for other genetic conditions is not assessed through screening.

**Positive Screen**

A positive screen for trisomy 21 is anxiety provoking and needs to be discussed with the patient in an environment that allows proper explanation and discussion of options. Allow sufficient time for the woman and her partner to ask questions.

The first point of counselling should be that there are a number of reasons why a screen may be positive. A positive screen is not a diagnosis of a chromosome anomaly; it is a positive screen as established by a predetermined cut-off, and further investigation and possibly invasive testing will be required. It may be necessary to discuss with the patient the false-positive rate of the tests used.

Counselling should include a discussion of risk. Patients often find it easier to understand risks when they are explained as percentages. For example, a risk of 1/100 is a 1% risk of the fetus having the condition whereas a risk of 1/200 is a risk of 0.5%. Stated another way, a risk of 1/200 means that there is a 99.5% chance that the fetus does not have trisomy 21 or that if 200 women have this same result, 1 of them will have a fetus with trisomy 21 and 199 will not. An explanation of a negative screen and the percentage of risk may also be helpful.

For women of advanced maternal age (≥ 35 years of age), screening may result in a woman's risk for aneuploidy being lowered but still result in a positive screen. This lowered risk may be acceptable to some women, but counselling is required to help women understand their risk and that they are eligible for invasive testing.

Counselling for a positive screen should review the patient’s options and should include a discussion about invasive testing, what the test will diagnose, the risk of the procedure, and why she may or may not wish to have the test(s). In the vast majority of cases, amniocentesis will provide a definitive answer as to whether or not the fetus has a chromosomal anomaly. Chorionic villus sampling is available in some centres in Canada and may be available for women who screen positive after first trimester biochemistry and/or nuchal translucency measurement.

In some centres in Canada, women with positive screens are referred for further ultrasound assessment, and the risk determined by serum screening is adjusted depending on the presence or absence of fetal soft markers. If a soft marker or markers are present, the risk is increased as determined by the likelihood ratio for the marker or markers present. The absence of any markers or anomalies may result in a lowering of the risk. Regardless of the risk adjustment from the ultrasound, women may still choose to have amniocentesis for a definitive diagnosis.
Counselling must include the information that if invasive testing does reveal a fetus has trisomy 21 or any other chromosomal anomaly, pregnancy termination may be an option. It should be made clear to the patient that the offer of invasive testing is not contingent upon her terminating the pregnancy if her baby has a chromosomal anomaly. It is important for women to understand that if a diagnosis of Down syndrome or other anomaly is made, further consultation and support will be available to help her decide whether to continue or terminate the pregnancy. Women and families may require more information about what trisomy 21 is and about the possible health implications and long-term outcomes for people with this condition. A request for consultation at a genetics service can be helpful. Also, diagnosing trisomy 21 or other non-lethal chromosomal anomaly prenatally ensures that the fetus receives the most appropriate prenatal and neonatal care, including testing and monitoring that may be necessary, such as fetal echocardiogram and increased antenatal and intrapartum surveillance.

Women should be made aware that although invasive testing is being offered, it is not mandatory following a positive screen. They should be reassured that they will still receive the best possible care they if they choose not to have diagnostic testing.

### TIPS FOR COUNSELING PATIENTS WITH A POSITIVE SCREENING RESULT

Tell your patient that

- A positive screen does not mean her baby is affected.
- Her risk for having an affected fetus has been adjusted from her age-only related risk and that her risk is higher than the pre-determined cut-off, which results in a positive screen.
- False positives do occur.
- She is eligible for diagnostic invasive testing, but this is her choice, and she can decline the procedure.
- If she has diagnostic testing following a positive screening result, it will diagnose Down syndrome and that other chromosome anomalies may be diagnosed.
- The identification of a chromosomal anomaly may require further investigation of the parents’ chromosomes before a firm diagnosis can be made.
- A positive screen does not warrant further genetic testing other than amniocentesis or chorionic villus sampling unless there are other indications for more in-depth testing on the basis of previous pregnancy history or family history.
- Chromosome analysis is specific; no other genetic testing is done unless indicated.
- The pregnancy loss risk associated with amniocentesis is 1:175 to 1:100.
- If she has a fetus diagnosed with a chromosomal anomaly, she has the option of continuing or terminating the pregnancy.
- If she chooses to continue her pregnancy, special tests, such as a fetal echocardiogram, will be performed as necessary, and routine obstetrical care will be adjusted because there is an increased risk for adverse outcome with a trisomy 21 affected pregnancy.
- This is a difficult and very personal decision and she will be supported whatever she chooses to do. Acknowledge that a positive screen is anxiety provoking and support the woman in her decision making.

### BIBLIOGRAPHY


