

ANEUPLOIDY SCREENING PROGRAM FOR SASKATCHEWAN

INFORMATION FOR HEALTH
CARE PROVIDER

2020

Newborn Screening
Roy Romanow Provincial Laboratory
Regina, Saskatchewan

What is Prenatal Screening for Aneuploidy and Open Neural Tube Defects?

Prenatal screening is a test or combination of tests available to all pregnant women. It is intended to identify women with an increased risk of having a fetus with certain congenital malformations or chromosomal abnormalities. The screening program can evaluate the risk of the fetus having Trisomy 21 (Down syndrome), Trisomy 18 or an open neural tube defect. Women with pregnancies identified as higher risk for these anomalies can then be offered a diagnostic test. The test is voluntary. All women regardless of age must be presented with adequate information in order to make a decision about whether to accept or decline testing. A patient education pamphlet is provided and should be given to the woman when counselling about prenatal testing takes place.

Screening vs. diagnostic testing

The program to be offered to women begins with screening tests and may then go on to definitive diagnostic testing. Some of the women and the families to whom testing is offered may not be clear about the distinction between the tests and as their health care provider you will have to ensure that they do understand the distinction.

Screening tests are intended to be offered to the entire population for the purpose of detecting those at increased risk of having a disease. Such tests are only intended to, and only can, determine what the chance is that a particular disease is present. Increased risk does not mean the presence of disease. It is not possible to have a positive or negative result from a screening test; therefore of course it is not possible to have false positives either. We report the results as **increased risk** or **decreased risk** although it is acknowledged that the terms positive and negative are used in some other programs.

Diagnostic tests will be done if the chance of the occurrence of disease is high enough to warrant the performance of the diagnostic test. These tend to be invasive and have some increased risk associated with their performance. Their use therefore is usually restricted to patients with a sufficiently high chance of the existence of disease. Diagnostic tests will give a positive or negative result.

What can the test screen for?

Trisomy 21 (Down syndrome)

Trisomy 21 is a common cause of severe mental disability in children. One in 800 newborns are affected by Trisomy 21. People with Trisomy 21 may have varying degrees of mental disability. Some will be able to lead semi-independent lives while others will be completely dependent. About 35 per cent of Trisomy 21 pregnancies will miscarry between the beginning of pregnancy and term. Ninety per cent of Trisomy 21 fetuses who reach term will survive the first year of life. About 40 per cent of neonates with Trisomy 21 will have a heart defect.

Trisomy 18

Trisomy 18 is a rare and usually fatal chromosomal abnormality. It occurs in one in 8000 births. About 90 per cent of Trisomy 18 pregnancies will miscarry between the beginning of pregnancy and term. These fetuses often have serious cardiac abnormalities, as well as severe growth restriction and mental handicap. More than 90 per cent die in the first year of life.

Open Neural Tube Defect (ONTD)

An open neural tube defect is a congenital malformation where the fetal spine does not close properly. It occurs in about 1-2 per 1000 births. Anencephaly, where the cerebrum is absent is almost always fatal within hours of birth. Spinal defects are associated with variable effect depending on the degree and level of the malformation. These neonates will require specialized care, hospitalization, and surgical interventions. The child will have various disabilities including weakness, paralysis, incontinence, hydrocephaly and may have mental handicap.

Elements of the test

Biochemistry

Certain chemicals made by the fetus and/or placenta are found in maternal serum during pregnancy. These will be found in somewhat different amounts in the blood of women carrying a fetus with Trisomy 21, 18 or an open neural tube defect compared to a normal pregnancy.

First trimester serum screening (PAPP-A and fβhCG) – 11 to 13 weeks and 6 days

Pregnancy associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotropin (fβhCG) are measured in the serum of pregnant women between 11 and 13 and 6/7 weeks. From these values and maternal age, the risk of Trisomy 21 and 18 can be calculated. These tests do not assess the risk for open neural tube defects.

Second trimester serum screening (quad screen) (AFP, E3, Inhibin and βhCG) – 15 to 20 weeks

Alphafetoprotein (AFP), estriol (E3), Inhibin and Beta human chorionic gonadotropin (βhCG) are measured in the serum of pregnant women between 15 and 20 weeks gestation. From these values and maternal age, the risk of Trisomy 21, 18 and open neural tube defect can be calculated. Preferably the test will be done just after 15 weeks to allow more time to respond to any detected increased risk at an earlier gestational age.

Ultrasound

Trisomy 21, 18 and open neural tube defect cause some characteristic differences of appearance. Some of these may be apparent as early as in the first trimester fetus.

Nuchal translucency ultrasound

Trisomy 21 usually causes increased subcutaneous fluid. This can be seen in the fetus as increased nuchal translucency. The nuchal translucency ultrasound scan is an ultrasound examination performed between 11 and 14 weeks gestation. From the measured thickness of the nuchal translucency combined with maternal age, the risk of chromosomal abnormality can be calculated. The ultrasound scan may also be used to accurately date the pregnancy, detect multiple pregnancy and certain major fetal abnormalities.

The midtrimester ultrasound

The midtrimester ultrasound, performed between 18 and 20 weeks includes evaluation for structural abnormalities and confirmation of gestational age. For neural tube defects, the ultrasound is definitive for the diagnosis of anencephaly and will detect all but the smallest spina bifida lesions. Fetuses with Trisomy 21 will display “markers” on an ultrasound examination at least half the time. (Markers are findings that may be present in normal fetuses but are more common in aneuploid fetuses, such as echogenic bowel). For the fetus with a given risk of Trisomy 21, the presence or absence of these markers will allow further individual calculation of risk. The absence of any markers means that the risk of Trisomy 21 can be reduced by half.

How are the tests performed?

Women who present for prenatal care **must be offered** prenatal screening regardless of maternal age. Women should be counselled that screening for fetal Trisomy 21 and 18 and ONTDs is available and provided with a patient information pamphlet. Discussion about the methods of testing available, the performance of the test(s) as well as the implications of having screening will follow. For women choosing to have screening done, the Prenatal Screening requisition is completed. Information about maternal age, menstrual history, weight, diabetes status and previous ultrasound scan reports is very important to proper interpretation of the test and must be included on the requisition. The serum sample may be drawn at any laboratory at the appropriate gestational age and sent to Roy Romanow Provincial Laboratory. The ultrasound scan must be booked with an accredited diagnostic imaging facility.

Depending on the gestational age at presentation the following options are available:

Option 1 - Patient presents before 14 weeks gestation

1. If the results indicate a high risk of aneuploidy, the caregiver will be notified and nuchal translucency ultrasound will be recommended. When both these elements of testing are complete, the first trimester

integrated aneuploidy report (FTIA) will be issued. AFP screening in the second trimester is still recommended to evaluate the risk of ONTD. (Figure 1)

2. If the results indicate a low risk of aneuploidy, no report will be issued until second trimester serum screening is completed and then a **second trimester serum integrated (STSI) report** will be issued reporting the risk of aneuploidy and open neural tube defect. (Figure 1) This combination is the preferred test in the Aneuploidy Screening Program.

3. The appropriately counselled patient may choose to have both first trimester biochemistry and first trimester ultrasound and thus complete her risk assessment (except for the second trimester AFP) in the first trimester. This will be reported as a **first trimester integrated aneuploidy report (FTIA)**. (Figure 2)

Option 2 - Patient presents 15-20 weeks gestation

Second trimester serum screening is offered between 15 and 20 weeks gestation. It is preferable to do the test as soon after 15 weeks as possible.

The risk of aneuploidy and ONTD is reported in a **second trimester serum screening (STSS) report**. (Figure 1)

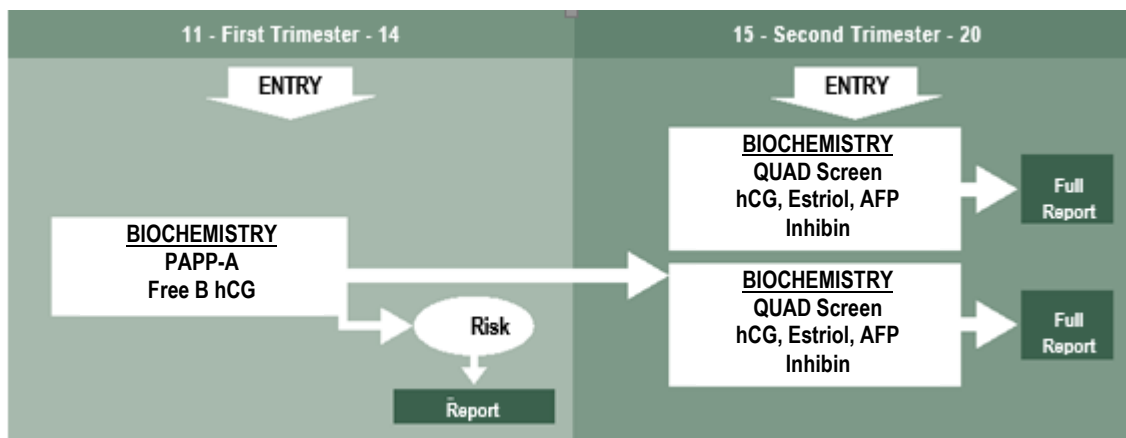


Figure 1: Aneuploidy Screening in Saskatchewan - The Biochemistry Option

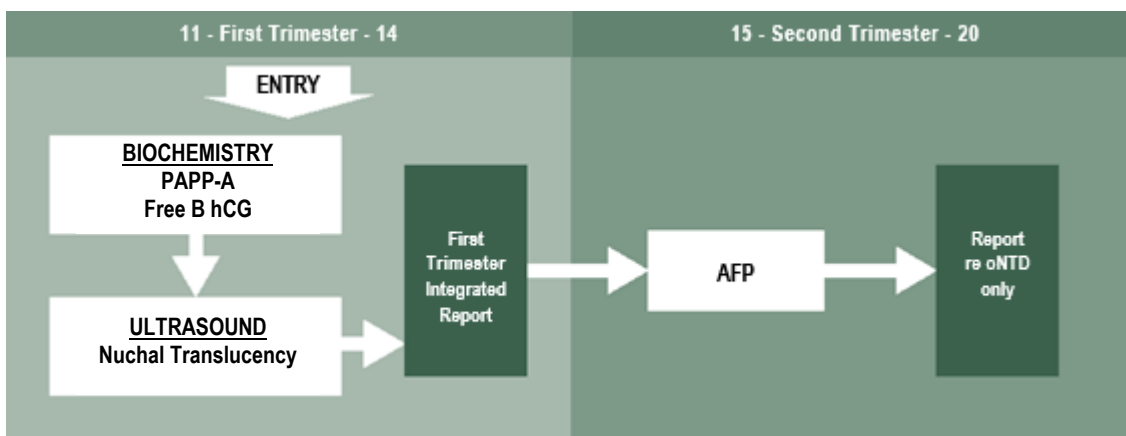


Figure 2: Aneuploidy Screening in Saskatchewan - The First Trimester Integrated Option

Option 3 - Patient presents after 20 weeks gestation

No serum screening may be offered at this gestation. Sonographic screening for fetal malformations should be offered.

Performance of the tests

The table below reports the detection rate of aneuploidy for the tests available (SOGC 2007):

TEST	COMPONENTS	GESTATIONAL AGE TEST IS PERFORMED IN WEEKS	DETECTION RATE	FALSE POSITIVE RATE	TEST PERFORMANCE*
Nuchal Translucency alone	NT	11-14	69-75%	5-8.1%	Inadequate alone
First trimester serum screening (FTSS)	PAPP-A & fβhCG	11-13 6/7	58%	5%	Inadequate alone
First trimester integrated aneuploidy	First tPAPP-A & fβhCG & Nuchal translucency	11-13 6/7	83%	5%	Meets criteria
First and second trimester serum integrated (STSI)	PAPP-A & fβhCG AFP, βhCG, Estriol, Inhibin	11-13 6/7 & 15-20	85%	4.4%	Meets criteria
Second trimester serum screening (QUAD SCREEN) (STSS)	AFP, βhCG, Estriol, Inhibin	15-20	77%	5.2%	Meets criteria

* According to current national guidelines, aneuploidy screening tests must detect $\geq 75\%$ of Trisomy 21 while identifying $\leq 5\%$ of the population as being of increased risk.

The maternal serum AFP level is used to determine the risk of ONTD. When the maternal serum AFP level is greater than 2.30 multiples of the median, the risk of ONTD is considered “above cut off”. Using this cut off, maternal serum AFP will detect about 80% of fetuses with ONTD with a false positive rate of 4-7%.

How will the test result be reported?

Results will indicate either increased or decreased risk for a fetus having aneuploidy or an open neural tube defect. Increased risk in this program is reported as “risk above cut off”. The overall incidence of Trisomy 21 at birth is about 1 per 800 deliveries at term for the whole population of pregnant women and increases with advancing maternal age to 1 in 385 for a 35 year old. In this program the cut off for risk of Trisomy 21 is defined as equal to the chance of occurrence of Trisomy 21 in women who would be 35 at delivery, which is 1 in 385. Decreased risk is anything less than that, and is reported as “risk below cut off”. The risk assessment is derived from the individual tests combined with maternal age and including the effect of maternal weight and insulin dependent diabetes status when relevant.

Action following a “risk below cut off” result

The care provider informs the patient. There is no further testing required. It is important that patient understands that this result does not guarantee a child without an anomaly.

Action following a “risk above cut off” result

The care provider informs the patient. Initial counselling will take place by the primary care provider and/or obstetrician and/or geneticist/genetic counselor. It is the responsibility of the care provider to provide the counselling and/or initiate any appropriate referrals. Follow up will vary depending upon increased risk for aneuploidy or ONTD.

“Risk above cut off” for aneuploidy (Trisomy 21 or 18)

Sonographic evaluation for fetal markers for aneuploidy may also be used to further refine risk but cannot offer definitive diagnosis. Invasive diagnostic testing, with some unavoidable risk, is required to make a diagnosis. This is most commonly an amniocentesis.

An amniocentesis is performed at 16 weeks or more and takes 2-3 weeks to get a karyotype result. The risk of pregnancy loss following amniocentesis is 1 in 200 to 1 in 400.

An alternative invasive diagnostic technique is chorionic villus sampling, offered in certain specialized centers at 11 to 13 6/7 weeks. It takes 7-10 days to get a karyotype result and is associated with a fetal loss rate of about 1%.

Counselling about the risks and benefits of invasive diagnosis is provided and the test is performed if the patient chooses.

“Risk above cut off” for ONTD

An appropriate detailed sonographic examination is indicated to identify structural anomalies. The AFP level may be increased in situations of ONTD, fetal abdominal wall defects, fetal demise, intestinal atresias, teratomas, fetomaternal transfusion, oligohydramnios or after invasive procedures.

If the sonographic examination provides an explanation and a diagnosis, further counseling and interventions are offered as indicated. If no obvious explanation is found, the pregnancy is at increased risk for obstetrical complications eg fetal growth restriction, hypertensive disorders in pregnancy. In these cases screening for these complications is indicated.

An approach to the patient

Every pregnant woman must be offered the opportunity to have screening and, if the risk is found to be high enough, diagnostic testing for the presence of aneuploidy. This is universal care for all pregnant women as prescribed by National guidelines. The problem is how to do this efficiently and effectively in already busy office schedules. The following are suggestions drawn from experience.

The purpose of aneuploidy screening is to help the pregnant woman, with her family, decide whether or not to have invasive diagnostic testing.

There is a lot of information that could be provided about the various screening tests including very fundamentally the difference between screening and diagnostic tests. If however the woman has already decided that she either will or will not have invasive testing (e.g. amniocentesis) then much of that detail is unnecessary and can be omitted.

The woman may have decided that she will have diagnostic testing for reasons that include:

- Her age is 40 or more (and thus her risk due to age alone is high enough that screening tests are unlikely to lower it below the level at which she would want an amniocentesis)
- There is another indication for amniocentesis such as a previous child with aneuploidy or the need for fetal cells for molecular diagnostic testing.

The woman has decided that she will not have invasive diagnostic testing because:

- She would continue the pregnancy anyway no matter what the results of invasive testing and thus would not accept (and would have a good reason not to be exposed to) the risks of amniocentesis or CVS.

If the patient would use the information from screening to assist her in making decisions or prepare for the birth, then, of course, it is both reasonable for her to get screening and necessary to provide information to her about the various screening options. This may be constrained somewhat by the gestational age at which the woman is first seen as well as the geographic location of the patient and access to certain tests, particularly ultrasound.

All of the screening tests seek to have a high detection rate while having as small a proportion as possible of the population identified as being at increased risk and thus potentially subjected to invasive diagnostic testing. Combining independent testing entities is a powerful way to enhance the detection rate while keeping the number of women declared to be at increased risk low, usually fixed at 5% or less.

The first trimester screening option

Neither first trimester biochemistry nor a first trimester ultrasound with nuchal translucency measurement perform well enough alone, because they do not have a high enough detection rate, so they should not be used in isolation. In combination however there is a high detection rate of 85-90% with a 5% increased risk group. The biochemistry must be done between 11 and 13 6/7 weeks. The ultrasound must be done between 11 and 14 weeks. This of course requires access to a unit which can do ultrasound and to do interpretations this unit must be certified by the Fetal Medicine Foundation or some equivalent and credible certifying body. Then the risk calculation from ultrasound and from biochemistry must be combined and a single result is given. Neither women nor their care providers should dwell on the calculated risk from any one part of the integrated test. The whole really is a better test than consideration of individual parts.

Amniocentesis: risks and limitations

Patients must be told there is a risk to the procedure which is conventionally considered to be about 1 in 200 to 1 in 400 for pregnancy loss. They also need to be told the two important limitations of the test.

1. A normal result does not necessarily guarantee a normal child but only a normal number of chromosomes. Most anomalies occur with normal chromosomes and so the frequent expectation of patients that an amniocentesis is a “test for everything” must be dispelled. In most instances the actual risk of other anomalies will be the normal 2-3% as it is for any couple without significant family history of anomaly and these risks are not increased with increased maternal age.
2. An abnormal result cannot be cured. The only benefits that could be provided to the woman from an amniocentesis in this circumstance therefore are knowledge during the pregnancy that she will have a child with special needs and she may feel that she can cope with this better if she knows what to expect; or choice, since she may choose termination of the pregnancy.

Acknowledgements

Special recognition goes to the following physicians who helped develop this information booklet:

- Dr. George Carson
- Dr. Marie Jocelyne Martel
- Dr. Kristine Mytopher
- Dr. Ian Suchet