Down Syndrome: Offer of Prenatal Diagnosis

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Key Points

- The likelihood of having a child with Down syndrome increases with maternal age.
- In addition, prenatal screening tests, using maternal serum and fetal ultrasound, are available to identify pregnancies in which the fetus has an increased likelihood to have Down syndrome.
- If maternal age at delivery will be 35 or older, or if a screening test is positive, prenatal diagnostic testing of cells derived from amniotic fluid can be used to determine whether the fetus has Down syndrome.
- Some people wish to pursue these testing options while others do not. Effective education and counseling helps ensure that a couple's preferences are identified and respected.

Learning Objectives

Participants will be able to:

- List the prenatal screening tests and diagnostic tests commonly available for the detection of Down syndrome;
- Explain why women/couples may opt for or against prenatal testing.

Family History Issues

- Chromosome abnormalities such as Down syndrome almost always occur as an isolated event, not likely to recur in a family. In such cases, Down syndrome occurs as trisomy 21, i.e. the presence of three separate copies of chromosome 21, instead of the normal two copies.
- In about 3% of cases, Down syndrome occurs because of an unbalanced chromosomal translocation. In these cases the third (extra) copy of chromosome 21 is attached to another chromosome. This cause of Down syndrome can occur as a chance event. However, about 25% of translocation cases occur as a result of inheritance of the translocation from a parent who carries a balanced translocation, in which one copy of chromosome 21 is attached to another chromosome. Although the parent's chromosome constitution is balanced, this

situation can result in the production of an egg or sperm carrying an extra chromosome 21, leading to Down syndrome. (See Robertsonian Translocation; Case 22, Risk Assessment.)

Red Flags 

Indicators of increased risk for Down syndrome include:

- A pregnancy in which the mother will be 35 years or older at the time of delivery;
- Maternal serum screening test results indicating an increased risk for Down syndrome;
- Ultrasound findings associated with Down syndrome (see Risk assessment, Other screening methods);
- A family or personal history of Down syndrome.

Case 21. A 36-Year-Old Woman Offered Prenatal Diagnosis for Down Syndrome

Mrs. G is a 36-year-old woman who is seen by her physician because she suspects she is pregnant. She and her husband have a 12-year-old daughter and a ten-year-old son.

Her pregnancy test is positive. An examination reveals an approximately six-week pregnancy. Her physician raises the possibility of prenatal diagnosis for chromosomal disorders because of Mrs. G's age. She is told that prenatal diagnosis would involve obtaining amniotic fluid by amniocentesis (usually performed between 15 and 18 weeks' gestation). The fetal cells obtained in the fluid would be cultured and a chromosome analysis would be performed. A similar diagnostic procedure, chorionic villus sampling (CVS) can be preformed earlier, at approximately 10-12 weeks' gestation. Both procedures involve a small risk of pregnancy loss, estimated at 1/200 to 1/400 for amniocentesis and 1/100 to 1/200 for CVS. Mrs. G states that she is uncomfortable with any invasive procedure, and she declines either CVS or amniocentesis.

A maternal serum triple screen test is ordered at 16 weeks' gestation. The results indicate a 1/90 likelihood of Down syndrome in the fetus. This is higher than Mrs. G's age-related risk of 1/287. Mrs. G is informed of the screening test results and prenatal diagnosis is again offered. She is anxious about these results but again declines prenatal diagnosis because of her concern about the risks associated with amniocentesis and her opinion that knowing the chromosome make-up of the fetus during pregnancy would not alter her decisions about the pregnancy or delivery.

Clinical Care Issues

Many women who are 35 years of age and older opt to have prenatal diagnosis for chromosome abnormalities. However, it is appropriate for the physician to provide an opportunity for discussion of the patient's and her partner's preferences before prenatal screening or diagnostic procedures are undertaken. This discussion should include how the results of such testing might influence decision making, and provides an opportunity to correct any unrealistic expectations about prenatal testing. For example, many individuals believe that having normal prenatal chromosome test results ensures a healthy baby. While the physician is obligated to offer prenatal testing for Down syndrome and certain other birth defects to all patients, the decision to pursue testing should be left to the patient. Patients decline prenatal diagnostic tests for many reasons, including concern over the procedure-related risk, moral or religious reasons, preference for minimal intervention, or perception of risk as not being high enough to warrant the procedure.

Risk Assessment

Prenatal screening

Several screening methods are available to determine whether a pregnancy is associated with an increased risk of Down syndrome.

Role of maternal age in assessing risk. The likelihood of having a child with a chromosome abnormality such as Down syndrome increases with maternal age. Down syndrome is the most common chromosome abnormality and constitutes about half of the overall risk at any maternal age (Table 1).

Table 1. Risk of Chromosome Abnormalities at Delivery, by Maternal Age

Maternal Age at Delivery	Risk of Down Syndrome	Risk of All Chromosome Abnormalities [1]
20 years	1/1923	1/526
30 years	1/885	1/384
35 years	1/365	1/178
40 years	1/109	1/63

1. Excluding 47, XXX

The prevalence of Down syndrome at birth is approximately 1 in 800. Although the risk is lower in younger women, approximately 80% of babies with Down syndrome are born to mothers under 35 years of age because younger women have more children.

Maternal serum screening for Down syndrome and other conditions. Maternal serum screening tests provide another opportunity to identify pregnancies in which there is an increased risk that the fetus has Down syndrome. Maternal serum screening tests use serum markers to estimate risk for Down syndrome and certain other conditions.

- The triple screen includes alpha feto protein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3).
- The quad screen add an additional marker, dimeric inhibin A, to the triple screen.

The maternal blood sample is typically obtained between 15 and 18 weeks of pregnancy. The values obtained from the laboratory analysis are corrected for gestational age, maternal age, maternal weight, ethnic background, and diabetic status. The results provide information about the risk of Down syndrome, neural tube defects (such as spina bifida), and trisomy 18 in the fetus. Low AFP, low uE3, high hCG, and high inhibin A are associated with an increased risk of Down Syndrome. Neural tube defects are associated with high AFP levels; trisomy 18 is associated with low levels of all four markers. The triple screen has a Down syndrome detection rate of approximately 60% with a false positive rate of 5%; the quad screen has a Down syndrome detection rate of about 70% with a false positive rate of 5%. For women over

age 35 years, both screening tests have a higher detection rate and a higher false positive rate.

Other screening methods. A mid-trimester ultrasound examination can also be offered to Mrs. G as a screening test for Down syndrome. This screening approach is a non-invasive method of evaluating the fetus and may provide some reassurance if the ultrasound is normal. However, a fetus with Down syndrome may not exhibit any ultrasound abnormalities. Additionally, the ability to identify Down syndrome varies by ultrasound facility. Several ultrasound markers are associated with an increased risk for Down syndrome including heart defects, cystic hygroma, echogenic bowel, short femur or humerus, and renal pylectasis. Some medical centers also consider an echogenic intracardiac focus to be associated with Down Syndrome. All of these findings may be visible as early as 15 weeks, but better visualization of the fetus is possible by 18 to 20 weeks. If one or more of these findings were present, Mrs. G could be offered amniocentesis to obtain fetal cells for chromosome analysis.

Tests under development for prenatal screening for Down syndrome are increasingly being offered in specialized clinics. These include:

- **Nuchal translucency measurement**, a first trimester ultrasound examination to screen for Down syndrome. This involves taking a measurement of the subcutaneous fluid-filled space at the back of the neck of the developing fetus. Such testing is typically performed between 11 and 13 weeks. If a fetus has Down syndrome, the measurement is often increased.
- **First trimester-only screening**, which includes a nuchal translucency measurement as well as first trimester maternal serum levels of two markers, pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (free beta-hCG). The detection rate is approximately 75% and the false positive rate is about 5%. Results are available within the first trimester. If the testing is timed precisely, results can be available when CVS is still an option for prenatal diagnosis.
- **Integrated screening**, which combines first trimester measurements of PAPP-A and nuchal translucency and the second trimester maternal serum quad screen. The integrated screen has the highest available detection rate (85%) and lowest false positive rate (1-3%) for the detection of Down syndrome.

Prenatal diagnosis

If any of the available screening methods indicates an increased risk of Down syndrome, prenatal diagnosis is offered, using either amniocentesis or chorionic villus sampling (CVS) to obtain fetal cells for chromosome analysis. Both procedures involve a small risk of pregnancy loss, estimated at 1/200 to 1/400 for amniocentesis and 1/100 to 1/200 for CVS [Verp 1992, Schemmer & Johnson 1993].

Role of family history in assessing risk

Because chromosome abnormalities such as Down syndrome usually occur sporadically, the role of family history in assessing risk for chromosome abnormalities is small. A lack of family history of the condition does not reduce a woman's age-related risk.

However, if a woman or her reproductive partner has a family history of Down syndrome, it is important to determine whether the affected individual has trisomy 21 or translocation Down syndrome (about 3% of Down syndrome cases). While trisomy 21 is not an inherited condition, translocation Down syndrome can be inherited. (See Case 22, Risk Assessment for more information.) If it is not possible to determine whether the affected relative had trisomy 21 or translocation Down syndrome, chromosome studies can be performed on the member of the couple who is related to the person with Down syndrome to determine if he or she carries a balanced translocation. Amniocentesis or CVS can detect both forms of Down syndrome in the fetus.

Genetic Counseling and Testing

Genetic counseling provides Mrs. G the opportunity to discuss the risk of Down syndrome and other chromosome abnormalities and prenatal screening/testing options. Information about Down syndrome will also be provided. Prenatal diagnostic procedures such as amniocentesis or CVS offer the family an opportunity to have chromosome testing done on the fetus to determine if the fetus is affected with Down syndrome. Such information would allow the parents to prepare for the birth of a child with Down syndrome or, if the parents choose, to terminate an affected pregnancy to avoid having a child with a chromosome abnormality.

Genetic counseling is traditionally non-directive; i.e., information about testing options and genetic risk is provided, but the genetic counselor does not provide a recommendation concerning the course of action to be taken. For Mrs. G, who does not desire pregnancy intervention or termination, genetic counseling would provide the opportunity to learn more about her risk, learn more about Down syndrome, and receive support for her decision to decline prenatal testing. Because Mrs. G is not interested in having a prenatal diagnostic test, early genetic counseling or a non-directive discussion of her options with her physician might have clarified her wishes; the triple screen test, and her resulting anxiety, might have been avoided.

Interventions

Preventive care

No methods exist to prevent the conception of a child with Down syndrome or other chromosome abnormalities.

Other clinical management

If Down syndrome is diagnosed prenatally by chromosome studies and the pregnancy is continued, a fetal echocardiogram is recommended at 20-24 weeks' gestation. Serial ultrasound examinations are also often done to monitor fetal growth and to evaluate the fetus for birth defects known to be associated with Down syndrome such as GI tract anomalies (e.g., duodenal atresia), which may result in polyhydramnios. In addition, comprehensive guidelines for the care of children with Down syndrome are available [Cooley 1991, AAP 2001] (see Case 22, Interventions).

Ethical/Legal/Social/Cultural Issues

Non-directiveness

Genetic counselors use non-directive, or client-centered, strategies to help the patient make the best personal decision based on accurate and complete information. This approach encourages the patient to take into account her values and preferences, as well as her partner's, in making a decision regarding prenatal diagnosis.

Legal obligation to offer screening / diagnostic testing

Offering prenatal diagnostic testing to women 35 years and older and offering prenatal maternal serum screening to women under 35 has become standard clinical practice. In some states, physicians have been sued for "wrongful birth" for not offering prenatal screening/ diagnostic testing for a pregnancy that resulted in the birth of a baby with Down syndrome. Parents argue that the physician is legally liable because the physician did not offer prenatal testing. Such suits have had varying outcomes, but the potential for litigation puts pressure on physicians to ensure that appropriate prenatal screening/diagnostic testing is offered and explained to their patients.

Resources

- **National Down Syndrome Society Web Site**
- **National Down Syndrome Congress**
- **National Library of Medicine Genetics Home Reference**
  Down syndrome
- **March of Dimes: Down Syndrome**
- **GeneTests Online Medical Genetics Information Resource**

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