

Understanding genetic screening for aneuploidy in pregnant women

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Introduction

Although mothers of advanced age, typically those who will be 35 or older on their estimated date of confinement (EDC) are at higher risk for having a fetus with aneuploidy or abnormal number of chromosomes, all pregnant women should be offered genetic testing for chromosomal anomalies. The most common aneuploidy is, of course, trisomy 21 commonly known as Down's syndrome. The overall prevalence of trisomy 21 is 1/700 term live births. There are two other relatively rare but still very important examples of aneuploidy, trisomy 18 or Edward's syndrome which occurs 1/8000 term live births and trisomy 13 or Patau syndrome which occurs 1/20000 term live births. Although there are isolated cases of affected children surviving for months and even years, both trisomy 18 and trisomy 13 are thought to be incompatible with long term postnatal survival.

Prenatal diagnosis of these chromosome problems allows women to make informed choices about continuing the pregnancy and helps prepare the neonatologists and pediatricians to be able to provide the extra care these children will need. Many will have malformations that require neonatal intensive care. In the case of a fetus with trisomy 18 or 13, mothers will have to decide how much intervention for fetal indications they want—if there is an abnormal result in the fetal monitoring, would she want a c-section understanding the very limited lifespan that the overwhelming majority of these fetuses have? Does she want fetal heart rate monitoring in labor? Mothers who are carrying a fetus with aneuploidy have an increased risk of pre-eclampsia due to abnormal placentation, especially those with a fetus who has trisomy 13. Treating those women with low dose aspirin, extra calcium supplementation and having them exercise for at least 20 minutes a day will help lower their risk. And, of course women faced with such a diagnosis have higher rates of depression and anxiety and will need additional support both antenatally as well as postpartum.

Ultrasound can help increase the suspicion that a fetus has aneuploidy. There are multiple "soft signs" of trisomy 21 and other signs that are more predictive such as an endocardial cushion defect. A fetus with trisomy 18 will commonly have signs such as clenched fists and so called rocker bottom feet. Because trisomy 13 is so devastating, it is virtually unheard of for such a fetus to have a normal ultrasound if the imaging is read by an experienced physician. A fetus with trisomy 13 will have midline facial defects as well as central nervous system malformations. Almost all fetuses with a major trisomy will have intrauterine growth restriction which is diagnosed by ultrasound. However, a fetus with trisomy 21 can also have a completely normal ultrasound so that is why other testing needs to be offered. Testing can be done in several ways. Testing is divided into screening tests where the results need to be confirmed with a diagnostic test and diagnostic tests. Screening tests that use hormone levels are offered several ways. Sequential screening is a stepwise approach where a woman has first trimester testing. If her risk is high, typically about 1/50 she is offered

a diagnostic test. Women with a low or moderate risk are offered a second trimester screening test and both results are used to calculate her risk. The other approach is contingency testing where a woman is offered first trimester screening and is only offered second trimester screening if she is in an intermediate risk group. Low risk women do not have any further testing.

Screening in the first trimester can be done by measuring the nuchal translucency or space behind the fetal neck. This space is enlarged in a fetus with aneuploidy and the larger the space the higher the risk. This obviously takes a skilled sonographer who must be certified in measuring the space. This nuchal translucency is combined with the measurement of two hormones obtained from a mother's blood: a Beta HCG and pregnancy associated plasma protein or PAPP-A. This test can only be performed in a narrow window typically between 11 0/7 weeks and 13 6/7 weeks. The false positive rate is 5% i.e. 5% of the time a mother is told she may have a fetus with a trisomy when the fetus is normal. If nuchal translucency ultrasound is not available, a mother can be offered PAPP-A testing in the first trimester and this is combined with other serum screening in the second trimester to give a final result. The detection rate for trisomy 21 is close to 90% but patients have to wait until the second trimester to get their final result. In the second trimester the mother can be offered serum screening which is the measurement of four hormone levels. This is typically performed around 16-18 weeks and most labs require it be drawn no later than 22 weeks. Below is a table showing the pattern of hormone results seen with the various trisomies. The serum screening is often supplemented with an ultrasound to look for some of the classic signs that fetuses with these trisomies have. Labs will report a patient's age related risk and then report how the screening tests changes those risks—whether it increases it or decreases it. These tests will detect about 75% of fetuses with trisomy 21 in women less than 35 and about 80 % of those who are 35 or older. The false positive rate is 5%. A false positive means the mother is told there is a problem when there is not. This test will detect about 60-80% of those with trisomy 18 with a false positive rate of 5%. It is not consider a good test to identify trisomy 13 but they will be identified by ultrasound findings.¹

Several variables such as maternal ethnicity, diabetes, weight and smoking can affect interpreting the results so most labs will require

information about these factors (Table 1). Another test that can be offered is cell free DNA, also a maternal blood sample. Cell free DNA is obtained by evaluating the DNA in trophoblasts or cells from the placenta. It is highly accurate and be obtained any time after about 9 weeks of pregnancy unless a mother is obese in which case most recommend obtaining it a few weeks later and the extra blood volume that an obese woman has can result in a “no call” or no result. Since a “no call” can also be due to aneuploidy, it is important not to confuse the picture by obtaining it too soon. This test will detect over 99% of fetuses with trisomy 21, over 97% of fetuses with trisomy 18 or

13. It has a very high negative predictive value, that is if the test is negative, it is very accurate in predicting that the fetus does not have the particular trisomy. However, patients should be advised that both false positives (she is told the result is positive but the fetus is normal) and false negatives (she is told the fetus has normal chromosomes when it does not) can occur. If a patient elects cell free DNA she should still have a second trimester maternal serum alpha protein as this can be a marker for congenital malformations and/or a pregnancy with a higher risk of stillbirth.

Table 1 Screening is less accurate in twin pregnancies and has a lower detection rate for trisomy 21

1 st trimester	Trisomy 21	Trisomy 18	Trisomy 13*
Nuchal translucency	Enlarged (≥ 3 mm)	Enlarged (≥ 3 mm)	Enlarged (≥ 3 mm)
Beta HCG	High	Low	Very Low
PAPP-A	Low	Low	Very Low
2 nd trimester			
Beta HCG	High	Low	* Not useful for trisomy 13 in the 2 nd trimester
Inhibin	High	Low	
Alpha fetoprotein	Low	Low	
Estriol	Low	Low	

The advantage of cell free DNA is it is highly accurate and can be offered at any time after 9 weeks whereas serum screening needs to be performed in a specific time and is not offered before 26 weeks or after 22 weeks. However, a low risk patient may not have insurance coverage for cell free DNA but would have it for serum screening. A positive result from one of these tests needs to be confirmed with a diagnostic test. One diagnostic test is a chorionic villus sample in which a needle is inserted into the placenta and a small sample is obtained. This is typically performed between 10 and 13 weeks. Another commonly used diagnostic test is an amniocentesis where a needle is inserted into the amniotic cavity and a small sample of amniotic fluid is obtained. This fluid contains fetal skin cells which are then used to perform an analysis of the chromosomes or a fetal karyotype.² This test cannot safely be performed before 16 weeks of pregnancy. It takes about 2 weeks to grow the chromosomes but it may take longer if the fetus has a trisomy since the cells are abnormal. The fluid is also generally sent for a fluorescent in situ or so called FISH analysis. This is a test where fluorescent probes that attach to chromosome 21, 18 or 13 are added to the fluid which is then examined under a microscope. If there are 3 probes seen for any of the 3 chromosomes, it helps to determine if there is an abnormality. This test is typically available in 3-4 days but patients should be advised that this is considered a preliminary result and they should not make any definitive decisions based on it. If there is a malformation seen on ultrasound, the fluid is sent for a microarray which is a more detailed evaluation of the chromosomes looking for small deletions that are not visible on the standard karyotype. Patients are counseled that there is about a 1/400 chance of losing the pregnancy as a result of the test including the possibility of losing a completely normal pregnancy. Another diagnostic test can be performed from the fetal blood obtained by inserting a needle into the umbilical cord and obtaining a small sample of fetal blood. However, this is rarely used for diagnosis of aneuploidy since it carries a higher risk of pregnancy loss.³

All patients should be advised of the possible tests that are available. Most genetic companies offer easy to read pamphlets generally available in both English and Spanish that explain the tests so that patients can read about them to help with their decision. All genetic counseling should be non-directive. That is, the patient should be presented with her options and she chooses to undergo the testing

that is consistent with her values. Some patients will want every test available and some will elect to have no testing. Even if a patient would not consider terminating a pregnancy should the fetus have a trisomy, she can benefit from the testing in that she and her and the baby's providers can be better prepared to care for both of them. And, of course, some patients who think they would not end a pregnancy change their minds when they are actually faced with a positive diagnostic test. She should check with her insurance company as to what benefits and coverage she has as some of the testing can be very expensive. Most will cover at least second trimester serum screening and one ultrasound since this is considered the standard of care. However, it is always a good idea for patients to be sure of their coverage which can sometimes affect their decision to have a particular test. Often companies that do genetic testing have programs to help lower the costs for patients who are self-pay. Patients can be advised to call and speak with a representative to see what might be available.

Conclusion

Genetic testing is a valuable part of good obstetrical care. It helps patients make informed decisions and to be better prepared for an adverse outcome. Generally speaking, patients will be given good news since most babies have normal chromosomes. It is always so rewarding to give a worried mother good news about her baby.

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Conflicts of interest

The author declares there are no conflicts of interest.

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