The Complete Guide to Prenatal Testing

written by: Amy Kiefer, PhD
& Molly Dickens, PhD

bloomlife

bloomlife

The Complete Guide to Prenatal Testing

Written by Amy Kiefer, PhD
& Molly Dickens, PhD

The Complete Guide to Prenatal Testing

Design by Patrick Scholz

Contents

Introduction:

Today, all pregnant women are offered prenatal genetic testing--a series of optional ultrasounds, blood tests, and invasive tests of fetal cells that can detect many common genetic disorders.

Understandably, many women feel conflicted about undergoing prenatal genetic testing. Every expectant mother hopes for a healthy, happy baby. Contemplating the possibility of a baby with a genetic defect can be stressful.

Let's say you decide on having some form of prenatal testing done. You then face yet another daunting decision--which tests are right for you? Until recently, pregnant women did not have much say in which prenatal tests they thought were most appropriate for them. Doctors made this decision largely based on a pregnant woman's age. Women under 35 were typically offered a hormone- and ultrasound-based screen. Women over 35 were offered amnio or CVS.

Then, in 2007, major medical organizations in the U.S. like the American College of Obstetricians and Gynecologists (ACOG) updated their guidelines to state that women, rather than their doctors, ought to choose which prenatal test or screen they wanted. Unfortunately, the decision process is often stressful, largely because we expect new parents to choose a prenatal test based on limited, sometimes conflicting, and sometimes inaccurate information key facts, like:

- How likely you, given your age and family history, are to carry a child with a genetic problem
- The accuracy of the different prenatal screens and tests
- The risk of miscarriage associated with CVS and amnio

Prenatal genetic testing is a personal decision. No one can tell you how to choose the best option for YOU. But the risks and benefits of each prenatal testing option can, and should, be easy to understand. We firmly believe this--**it's why we wrote this e-book.**

We want to help new parents understand prenatal genetic testing, to help them parse what can at first seem like a dizzying array of choices and decisions. We believe that no expectant parent should have to rely on gut reactions or other people's--potentially misinformed--opinions to choose a prenatal test.

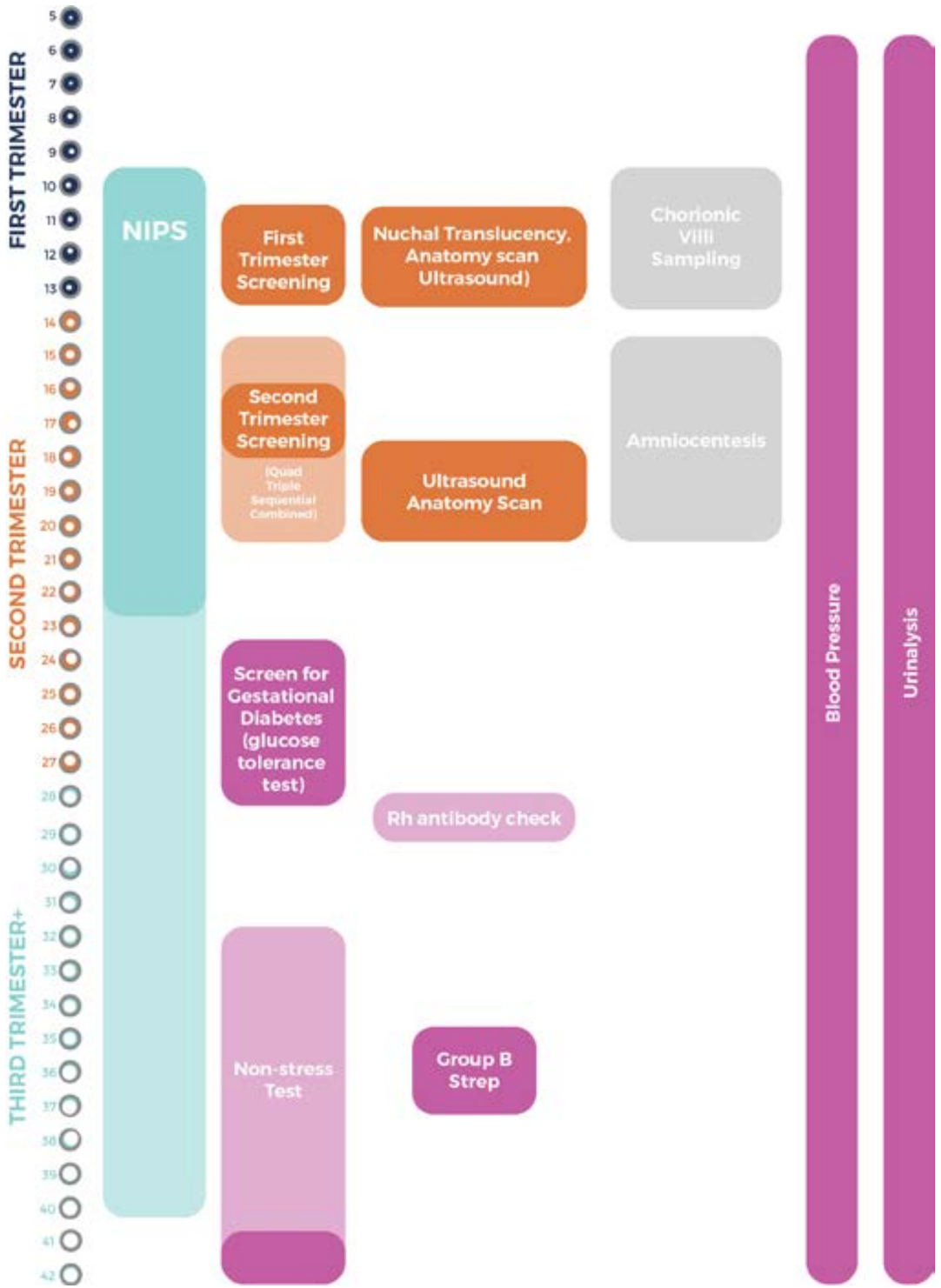
Yes, we will also give you a quick overview of every poke and prod you'll be subjected to during your pregnancy (see Chapter 1) but the main focus of this e-book is to lay out the benefits and drawbacks of each genetic testing option based on the best and latest scientific information available.

Since a key component is *your* baseline risk of having a child with various genetic disorders, we also delve into your likely risk of having a child with a genetic disorder. (Spoiler: the risk is not the same for every pregnant women, and age is not the only factor to consider.)

We hope this e-book helps you navigate these choices and make the best decision for you and your growing family.

1 Overview of Prenatal testing:

Prenatal Testing Timeline



TRADITIONAL GENETIC SCREENING

First Trimester Screening:
(Blood test, Nuchal Translucency and Anatomy Scan Ultrasound)
11-13 weeks

Second Trimester Screens:
(Triple, Quad, Sequential and Combined)
15-20 weeks - most accurate between 16-18
Anatomy Scan Ultrasound - 18-20 weeks

NON-INVASIVE PRENATAL SCREENING (NIPS):
(Upon request or recommendation)
10 -22 weeks, typically, but can be done up until delivery

INVASIVE GENETIC TESTING:
(Upon request or recommendation)

Amniocentesis:
15-20 weeks

Chorionic Villi Sampling:
10-13 weeks

ADDITIONAL TESTING:

First Trimester Blood Work: 6-12 weeks

Screen for Gestational Diabetes (glucose tolerance test):
24-28 weeks

Group B Strep (GSB): 35-37 weeks

Blood Pressure: weeks 6-40+

Urinalysis: weeks 6-40+

Rh antibody check:
28-29 weeks if necessary

Non-stress test (NST): starting between weeks 32-34 for pregnancies at high risk of stillbirth, as early as 26-28 weeks for especially high risk or multiples, weeks 40+ for post-due pregnancies

Brief Overview of Prenatal Tests:

Buckle up, dear pregnant friend, you are in for a whole lot of poking and prodding. Although the this book focuses on the genetic screens and tests for the health of the baby, we wanted to provide a quick overview for all the other tests that you may (or may not) encounter in the weeks ahead.

Genetic Screening/Testing:

Traditional Screens - Combines results from blood tests and anatomy scans during the first and second trimester. Provides you with a risk estimate, telling you how your baby is to have trisomy 21, 18, or 13. Read more in Chapter 2 and 3.

Noninvasive Prenatal Screening (NIPS) - Only given upon request or recommendation. Currently, doctors may only prescribe this type of genetic test if you are over 35. This type of test requires a blood draw and detects Down Syndrome, Trisomy 18, and Trisomy 13. Read more in Chapter 5.

Invasive Tests - This classification of genetic testing includes Chorionic Villi Sampling and Amniocentesis and require extracting fetal cells with a needle from the placenta (CVS) or from the amniotic fluid (amnio). These tests are the only truly diagnosic tests for genetic abnormalities. Read more in Chapter 6.

First Trimester Blood Work:

Complete Blood Count (CBC) - Assesses the numbers of the different types of cells in your blood. Red blood cell number may reflect a state of anemia (low iron), white blood cells can indicate how your body will handle illness, and platelet number can show whether you are at risk for blood clotting issues.

Blood Type - Determines whether you are Rh positive or negative. Rh factor is a protein that attaches to your red blood cells. If you and baby are both positive or both negative, you are all set. If you are negative and baby is positive, your body might make antibodies against Rh factor and cause problems for a subsequent pregnancy with an Rh-positive baby. When this is the case, you will have another test at the beginning of your third trimester to test for Rh antibodies (see Rh antibody test below)

Rubella - Tests to determine if you have previously been infected or received an immunization. Infection with Rubella (German measles) can cause serious birth defects.

Hepatitis B (and maybe C) - These viruses can pass through the placenta so this tests checks in on when or not you are infected.

STI's - Yup, you'll be checked for Syphilis and Chlamydia since these sexually transmitted infections can lead to complications. Isn't pregnancy fun?

Read more about all of these tests here:
http://www.acog.org/Patients/FAQs/Routine-Tests-During-Pregnancy

Urine tests:

Urinalysis - Checks for red blood cells that may indicate a urinary tract disease, white blood cells that could indicate a urinary tract infections, glucose an early indicator of gestational diabetes, and protein to compare to later protein tests that will check for preeclampsia risk.

Urine Culture - Assesses bacteria, an indication of a urinary tract infection

Second Trimester Blood Work:

CBC repeat - checking in again on all the parameters listed above.

Gestational diabetes screen (Glucose tolerance test): Between weeks 24-28, typically, but sometimes earlier if other risk factors are present. The general gist of this test is to measure how your pregnant body metabolizes sugar, an indicator that you may be at risk for gestational diabetes. Read more about this test here: http://www.acog.org/Patients/FAQs/Gestational-Diabetes

Rh antibody test: Weeks 28-29 if you tested negative for Rh factor. This tests for antibodies in your bloodstream. A negative result will prompt a shot with Rh immunoglobulin which will prevent your body from making Rh antibodies. A positive result may necessitate special care.
Read more about this test here: http://www.mayoclinic.org/tests-procedures/rh-factor/basics/definition/prc-20013476

Group B Streptococci (GBS):

Between 35-37 weeks. One out of four women carry around a this pesky little GBS bacteria in their vagina and/or rectum. Given its commonality and potentially devastating consequences for the newborn (albeit, incredibly rare), medical professionals advice administration of antibiotics when labor begins for GBS positive women. Since this bacteria comes and goes in the body, testing is done as close to due date as possible. It involves a quick swab of the skin around your vagina.
Read more about this test here:
https://www.cdc.gov/groupbstrep/about/fast-facts.html

Blood pressure checks:

Every time you visit your healthcare provider you will see that blood pressure cuff. Your blood pressure is very important for baby's health and development and elevated blood pressure (hypertension) needs to be monitored closely. In addition, blood pressure is often the first sign of preeclampsia, a life-threatening pregnancy complication. Read more here: http://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy/art-20046098

Additional Urinalysis:

Depending on your healthcare provider, you may be peeing in a cup each and every visit (or at least for the last trimester.) In addition to monitoring your sugar to spot signs of gestational diabetes, testing your urine for protein is also a warning for preeclampsia Read more here: http://www.mayoclinic.org/diseases-conditions/preeclampsia/basics/tests-diagnosis/con-20031644

Nonstress tests:

This test monitors baby's motion in utero and are typically conducted between 32-34 weeks for pregnancies at high risk of stillbirth, or as early as 26-28 weeks for especially high risk or multiples. If you are not in either category but go past your due date (ugh), you may be sent to get these regularly after 40 weeks. Read more about this test here: http://www.aafp.org/afp/2000/0901/p1184.html.

Prenatal Genetic Testing: Pro's and Con's Cheat Sheet

Traditional Screens

(The First Trimester Screen, Quad Screen, Triple Screen, and Integrated Screen)

Pros

- Requires only a blood draw and an ultrasound at 11-13 weeks
- No increased risk of miscarriage
- Results are well understood by most medical professionals
- Can pick up on some chromosomal abnormalities not covered by NIPS, such as mosaicism and certain structural abnormalities.

Cons

- Not as accurate as NIPS (see below) at detecting the 3 most common trisomies (21, 18 & 13) or sex chromosome aneuploidies.
- Has a much higher rate of false alarms than NIPS. About 1 in 20 women will receive a "positive" and over 90% of these will turn out to be false alarms.
- Most accurate when a combined risk is given at 17-18 weeks, but this requires waiting until the second trimester for a final risk assessment
- The rate of false positives increases with age. By age 40, about a third of women will receive a positive; after age 43, over 90% of women will receive a positive.

Non-Invasive Prenatal Screening (NIPS)

Pros

- Done as early as 10 weeks
- No increased risk of miscarriage
- Requires only a blood draw
- More accurate than traditional screens at detecting the three major trisomies (21,18, & 13) and sex chromo some aneuploidies
- Fewer false alarms than with traditional screens

Cons

- Like all screens, not diagnostic--may miss some diagnoses and raise false alarms.
- All positive results need to be confirmed with an invasive test.
- Does not cover all genetic problems, only the three major trisomies and sex chromosome aneuploidies
- Does not test for spina bifida--additional screening for spina bifida at 15-18 weeks is still recommended

Invasive Tests: Chorionic Villus Sampling

Pros

- Done early (10-13 weeks)
- Comprehensive -- covers all currently detectable genetic disorders, including rare trisomies, struc tural rearrangements of small pieces of individual chromosomes (deletions, duplications, and translocations), and certain single gene disorders like cystic fibrosis and sickle cell anemia

Cons

- Small increase in risk of miscarriage. Current estimates, however, put this risk at less than 1 in 400 (see Risk of Miscarriage from Invasive Tests)
- 1 in 100 chance of a mosaic result (a mix of abnormal and normal cells; 80% of the time the baby is genetically normal and mosaicism is confined to the placenta. This result should be confirmed by amniocentesis, which relies on fetal not placental cells.)
- Does not cover spina bifida; second trimester blood screen still recommended
- Small chance (about 1%) of uncovering a genetic variant of unknown effect

Invasive Tests: Amniocentesis

Pros

- Comprehensive -- covers all currently detectable genetic disorders, including rare trisomies, structural rearrangements of small pieces of individual chromosomes (deletions, duplications, and translocations), and certain single gene disorders like cystic fibrosis and sickle cell anemia

Cons

- Small increase in risk of miscarriage. Current estimates, however, put this risk at less than 1 in 400 (see Risk of Miscarriage from Invasive Tests)
- Done after the first trimester (between 15-20 weeks)
- Small chance (about 1%) of uncovering a genetic variant of unknown effect

Traditional Screens:

2

First Trimester Screen

First Trimester Screen:

Overview

The first trimester screen provides you with a risk estimate. It tells you how LIKELY your baby is to have trisomy 21, 18, or 13 based on:

- Your age
- Your baby's fetal nuchal translucency (NT) - an ultrasound measurement of the amount of fluid in the back of your baby's neck
- The levels of two pregnancy hormones in your blood: free β-human chori onic gonadotrophin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A)

These hormones and the nuchal translucency measurement correlate--imperfect-ly--with fetal genetic abnormalities. They give an idea about how likely you are to be carrying a baby with a genetic problem, but they cannot tell you for sure whether or not your baby is affected. [1][2][3]

Results of the first trimester screen usually return within a week. Results contain two pieces of information: (1) a risk estimate and (2) whether that estimate is "positive" or "negative" for any of the three trisomies

When you're told of risk estimate being "positive" or "negative", keep in mind that this designations is based on an arbitrary cut-off. It simply tells you whether your risk is higher or lower than a predetermined threshold (for example, 1 in 250) [4]. By itself, this result does not tell you whether your baby has--or does not have--a particular genetic disorder.

Since the threshold used to determine a "positive" screen can vary from doctor to doctor, it's might be helpful to ask your provider what cutoff they use. This cutoff may differ from your own sense of what is a high or low risk.

Risk Estimate

The risk estimate comes from large studies that profiled hormones and ultrasound measurements in thousands of pregnant women. This estimate tells you the percent-age of people with hormones and NTs similar to yours who were carrying a baby with a trisomy in these earlier studies. For example, you may be told that you have a 1 in 1000 of having a baby with Down Syndrome (trisomy 21). The risk can range anywhere from under 1 in 10,000 to as high as 1 in 2.

Receiving a Positive

If you get a positive screening result, take a deep breath! On average, 1 in 20 pregnant women will receive a "positive" on the first trimester screen. The vast majority of these "positives" (over 90%) are false alarms.

Again, a positive result only implies that your risk is higher than the prespecified cutoff--meaning that further testing, either with amnio, CVS, or Non-Invasive Prenatal Screening (NIPS) may be warranted.

Receiving a Negative

Receiving a negative means your risk of having a baby with one of the three most common trisomies is lower than the set cutoff of, say, 1 in 250. This is certainly good news.

That said, a negative result does not guarantee a healthy baby. The first trimester screen misses anywhere from 15-30% of babies born with trisomy 21, 18, and 13. The first trimester screen also does not detect many rare chromosomal disorders or other birth defects. The chances of having a genetic disorder go undetected are about 1 in 2,000 [5]. If this tiny possibility concerns you, you have options for additional testing (that's what we're here for!)

Advantages of the First Trimester Screen

- Completed in the first trimester

- No increase in the risk of miscarriage

- Detection of other birth defects: The first trimester ultrasound for NT at 11-13 weeks can also detect other birth defects, such as many heart and abdominal wall defects and anencephaly (a severe spinal defect in which the majority of the brain fails to develop.) According to one study, this first trimester ultrasound picks up approximately 70% of the major anatomical defects (those that require surgery shortly after birth or will not support life. (Note: ACOG now recommends a first trimester ultrasound regardless of whether you choose the first trimester screen.)

Drawbacks of the First Trimester Screen

- Not diagnostic. The first trimester screen only provides a risk estimate, not a diagnosis. As a result, it...

    - Misses anywhere from 10-30% of fetuses with one of the three most common trisomies, Down Syndrome and Trisomy 13 and 18.

• Has a high rate of false alarms (false positives).
The majority (over 90%) of "positives" turn out to be false alarms. All positives should be confirmed with invasive testing.

• May miss rare genetic abnormalities. The first trimester screen de tects only 65-80% of genetic problems covered by invasive testing (am-niocen tesis or CVS) [6]

• Age Matters. The mother's age affects the first trimester screen's detection and false positive rates.

• Younger women receive a higher percentage of false negatives than older women. For women under 35, the first trimester screen fails to detect about 25% of trisomies, whereas for women 35 and over, the first trimester screen fails to detect about 10% of trisomies. Although women under 35 are less likely to carry a baby with trisomy, they should understand that the first trimester screen detects fewer than the oft-quoted 85% of trisomies for them. The 85% figure is based on the combined detection rate for all women.

• Older women are more likely than younger women to receive a false positive. A 40-year-old woman has a 30% or higher chance of a positive screening result based on her age alone. For women age 44 and older, [7] will receive a positive result. Women in their 40s may want to bypass the first trimester screen in favor of amnio, CVS, or NIPS, since a positive is basically a foregone conclusion.

Mother's Age	Percentage Receiving a Positive on the First Trimester Screen
40	30%
43	63%
44	70–90%

Source:[7] http://www.ncbi.nlm.nih.gov/pubmed/25330685

* * *

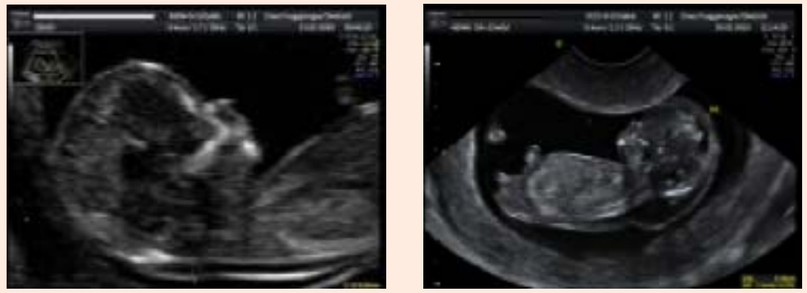
Special Topics:

How is the first trimester screen risk estimate calculated?

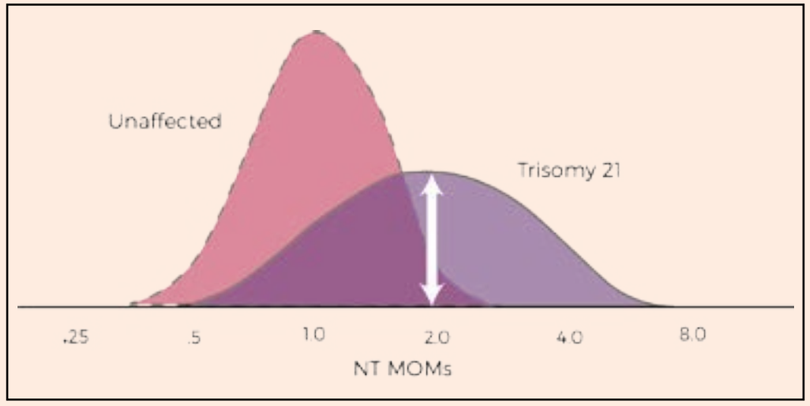
Certain hormones and ultrasound measurements tend to differ between babies with specific genetic disorders and healthy babies. The first trimester screen uses these correlates of genetic disorders to calculate a risk estimate for your baby.

Fetuses with Down Syndrome often have a larger-than-normal nuchal translucencies (NTs), but not 100% of the time. On the flip side, some healthy babies have larger-than-average NTs.

The image below shows a fetus with a normal NT at the first trimester ultrasound (left) and a fetus with a larger-than-normal NT (right).

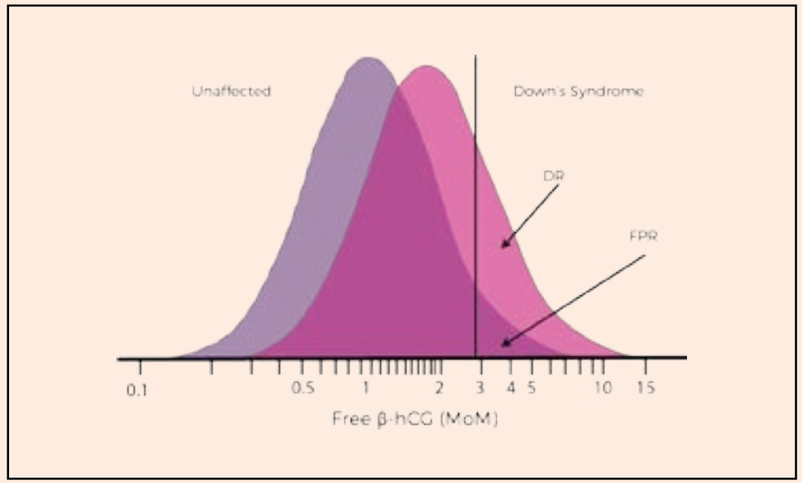


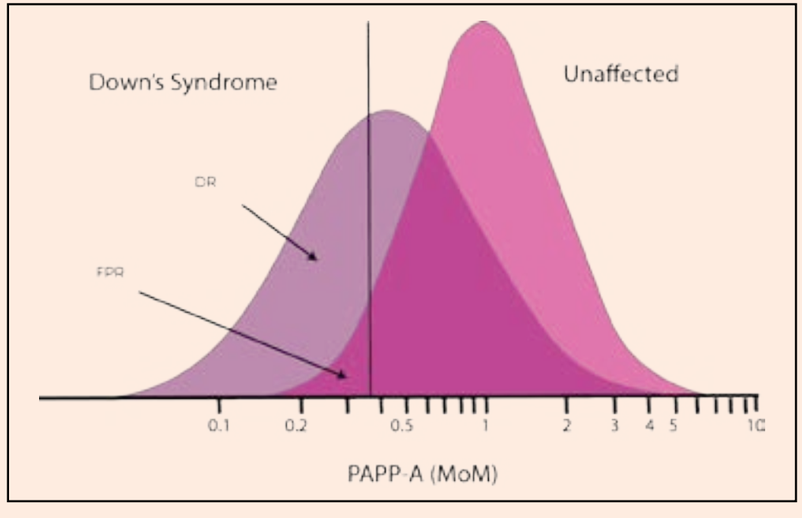
The graph below shows the expected range of NTs in fetuses with Down Syndrome and unaffected fetuses. As you can see, there's a fair amount of overlap in NTs between healthy babies (Unaffected, shown in pink) and those with Down Syndrome (shown in dark purple).



SOURCE: adapted from http://www.wardelab.com/20_2.html

The same is true for the blood-based hormones used in the first trimester screen. β-hCG tends to be higher than normal in Down Syndrome and PAPP-A tends to lower than normal, but not 100% of the time.





SOURCE: adapted from http://www.wolfson.qmul.ac.uk/images/pdfs/riskcurves.pdf
β-hCG and PAPP-A are often lower than normal in the other two most common trisomies, trisomy 13 and trisomy 18, but again not 100% of the time.

The first trimester screen uses these correlates of genetic disorders to calculate a risk estimate for your baby.

Unfortunately, because affected and unaffected pregnancies can have the same hormonal and ultrasound characteristics, the first trimester screen has a high rate of false positives (5%) and a high rate of missed diagnoses (15-30%).

One way to improve the first trimester screen's accuracy is to combine it with hormonal measurements performed early in the second trimester as part of the triple or quadruple screens. When combined with the first trimester screen, these second trimester measurements boost the detection rate for Down Syndrome to 95% while decreasing the false positive rate to under 5%.

One downside to this approach is that it pushes your final risk estimate out to 17-19 weeks.

Traditional Screens:

(Triple and Quadruple Screens)

3

Second Trimester Screen

Second Trimester Screen:

Overview

The triple screen provides a risk of Down Syndrome and trisomy 13 and 18 based on the level of three hormones in your blood:

- Alpha fetoprotein
- HCG
- Unconjugated estriol

The quadruple screen relies on these three hormones, plus an additional blood based-hormone: inhibin A.

The triple screen alone (not in combination with the first trimester screen) detects an estimated 69% of cases of Down Syndrome. The quadruple screen alone detects an estimated 81%.

Advantages

- Provides an option for women who miss or skip first trimester screening
- Requires only a blood draw
- No increased risk of miscarriage
- Gives risk estimates not only for trisomies 21, 18, and 13, but also for spina bifida and for a rare genetic disorder known as Smith Lemli Opitz Syndrome. (Smith Lemli Opitz Syndrome affects between 1 in 20,000 to 1 in 60,000 babies. The disorder is most common in Europeans of Central European ancestry and virtually unheard of in people of African or Asian ancestry.)

Integrated Screen

The results of the triple or quadruple screen are often combined with those of the first trimester screen to give a single composite risk estimate.

When a combined risk estimate is reported after the triple or quadruple screen results return, this approach is called integrated screening. When an initial risk estimate is given after the first trimester screen, followed by a revised estimate after the triple or quadruple screen results return, this approach is called stepwise sequential screening.

Traditional Screens:

4 Comparing the Options

Traditional Screens:

Comparing the Different Options:

Of all the possible traditional screens, the integrated screen is the most accurate for the three most common trisomies, detecting somewhere between 90-96% cases of Down Syndrome [8]. This estimate comes from the First- and Second-Trimester Evaluation of Risk (FASTER) trial, a large study conducted at 15 U.S.-based prenatal centers from 1999 to 2002 [8].

The table below shows how well each screen detected Down Syndrome in this trial:

Screen Performance at Detecting Down Syndrome in the FASTER Trial (All women):

Screen	Detection Rate	False Positive Rate
First trimester combined screen	86%	5.6%
Triple Screen	78%	5%
Quadruple Screen	86%	5%
Integrated Screen (first trimester combined screen and quadruple screen)	95%	4%

Source: http://www.nejm.org/doi/full/10.1056/NEJMoa043693#ref6=&t=articleBackground (Malone et al., 2005 NEJM)

(Note: These above estimates apply only to women carrying singletons. Pregnancies involving twin and higher order multiples were excluded from the study.)

The above detection and false positive rates may look familiar, as these rates are the ones typically stated in the info you receive from your doctor about the various prenatal testing options.

But there is an important, and often overlooked, caveat to those percentages: **They are average rates for all pregnant women.** These rates may not apply to you, because your age changes the risk calculation. In other words, your ages affects the detection and false positive rates of these screens [8].

According to the FASTER trial (which uses 35 as a cut point):
Women over 35-- you are more likely to receive a false positive but less likely to have missed diagnosis.
Women under 35--you are less likely to receive a false positive than older women, but you have a higher chance of a missed diagnosis.

Detection of Down Syndrome for women under 35 in the FASTER trial:

Screen	Detection Rate	False Positive Rate
First trimester combined screen	75%	5%
Quadruple Screen	77%	2.3%
Integrated (first trimester combined screen and quadruple screen)	77%	0.4%

Detection of Down Syndrome for women over 35 in the FASTER trial:

Screen	Detection Rate	False Positive Rate
First trimester combined screen	95%	22%
Quadruple Screen	92%	13%
Integrated (first trimester combined screen and quadruple screen)	91%	2%

Alternatives to Traditional Screens

CVS or amniocentesis were once the only alternatives to traditional screens. But in 2011, Non-Invasive Prenatal Screening (NIPS) became available.

NIPS has numerous advantages. It can be done as early 10 weeks. It offers a much lower chance of a false positive. And it requires only a blood draw.

So it's no surprise that in only 5 years, NIPS has rapidly reshaped the prenatal testing landscape.

Like traditional screens, NIPS assesses your risk for Down Syndrome, Trisomy 18, Trisomy 13, and the sex chromosome aneuploidies. NIPS cannot tell you for certain whether your baby has these genetic disorders, but it has a much higher detection rate and a lower false positive rate than any of the traditional screens.

Despite the higher detection rate and lower false positive rate, there are several potential drawbacks with NIPS. Many women and some doctors are not adequately informed of these, so we cover them in depth in Special Topics: Criticisms of NIPS--justified or not?

5

Non-Invasive Prenatal Screening (NIPS)

Non-Invasive Prenatal Screening (NIPS):

Overview

Non-Invasive Prenatal Screening (NIPS) became available in 2011, and pregnant women began clamoring for these tests.

It's easy to see why: NIPS boasts a much higher detection rate and lower false positive rate for the three most common trisomies (21,13, and 18) than those of traditional screens.

Like traditional screens, NIPS does not increase the chances of miscarriage. NIPS requires only a simple blood draw, can be done as early as 10 weeks, and (bonus!) can tell you your baby's sex with greater than 99% accuracy [9]

All NIPS tests on the market can detect Down Syndrome, Trisomy 18, and Trisomy 13. Upon request, they will also test for sex chromosome aneuploidies, including monosomy X (Turner Syndrome), XXY (Klinefelter's Syndrome), and XXX (Triple X).

A few NIPS tests also can detect a handful of rare chromosomal abnormalities (See Which NIPS Test is Right for You? to learn more about testing for rare abnormalities.)

Results

Results typically return within 3 days.

Like other screens, NIPS provides a risk estimate, not a diagnosis. Risk estimates higher than a predetermined cutoff, usually 1 in 100, are reported as positive.

Receiving a Positive

A positive means that you are at increased risk of carrying a fetus with a chromosomal abnormality.

The chance that your fetus actually has that genetic disorder given a positive result (what medical professionals call the positive predictive value) depends on your age.

The table below shows the positive predictive value (the chance a positive is a true positive) at age 25 and age 40 for the three most common trisomies.

	Age 25	Age 40
Trisomy 21	33%	87%
Trisomy 18	13%	68%
Trisomy 13	9%	57%

Source: ACOG's Committee Opinion: Cell-free DNA Screening for Fetal Aneuploidy

Additional sources: http://www.ncbi.nlm.nih.gov/pubmed/25843063

For sex chromosome abnormalities, the positive predictive value ranges from 20-40%.

For other rarer chromosomal abnormalities like microdeletions, the positive predictive value is lower: A positive will turn out to be a true positive less than 10% of the time [10].

(Why does the positive predictive value depend on age? Age does not affect test accuracy, as you might assume. Instead, your age affects your baseline risk, which in turn influences the positive predictive value. Younger women, for example, are less likely to carry a fetus with a trisomy, and thus are more likely to receive a false positive [11].)

The key point: Although NIPS has much higher accuracy and far fewer false positive than traditional screens (less than 1%), a significant fraction of NIPS positives turn out to be false positives, because these chromosomal abnormalities are rare.

Physicians and major medical organizations like the American College of Obstetricians and Gynecologists and the American College of Medical Geneticists therefore recommend confirming positives with invasive testing before terminating a pregnancy.

Receiving a Negative

Receiving a negative means your risk of carrying a baby with Down Syndrome, trisomy 13, and trisomy 18, or a sex chromosome abnormality is low. The chances are so low, in fact, that we cannot say exactly how often NIPS misses an affected fetus (a false negative), over than to say that the chances are less than 1 in 2000.

Still, false negatives have occurred [12]. A negative implies your risk of the tested for disorders is extremely low--but not zero.

Special Topics:

How NIPS Works

During pregnancy, small DNA fragments known as cell-free DNA pass from your baby's placenta into your bloodstream.

NIPS laboratories analyze these cell-free DNA fragments to calculate how likely your fetus is to have trisomy 21, 13, or 18.

Like other prenatal screens, the labs adjust the results of the DNA analysis based on other risk factors like the mother's age.

Accuracy= Detection Rates, False Positive Rates, and Positive Predictive Values

Many people claim that NIPS has 99% accuracy. But by itself, this statement is meaningless.

NIPS does detect 99% of cases Down Syndrome. But this absolutely does not imply that a positive is correct 99% of the time.

Your baseline risk--mainly determined by your age--also influences what physicians call the positive predictive value--the chances that positive NIPS result is a true positive. This chance ranges from around 30-90%. A range far below 99%!

NIPS Positive Predictive Values by Age and Trisomy

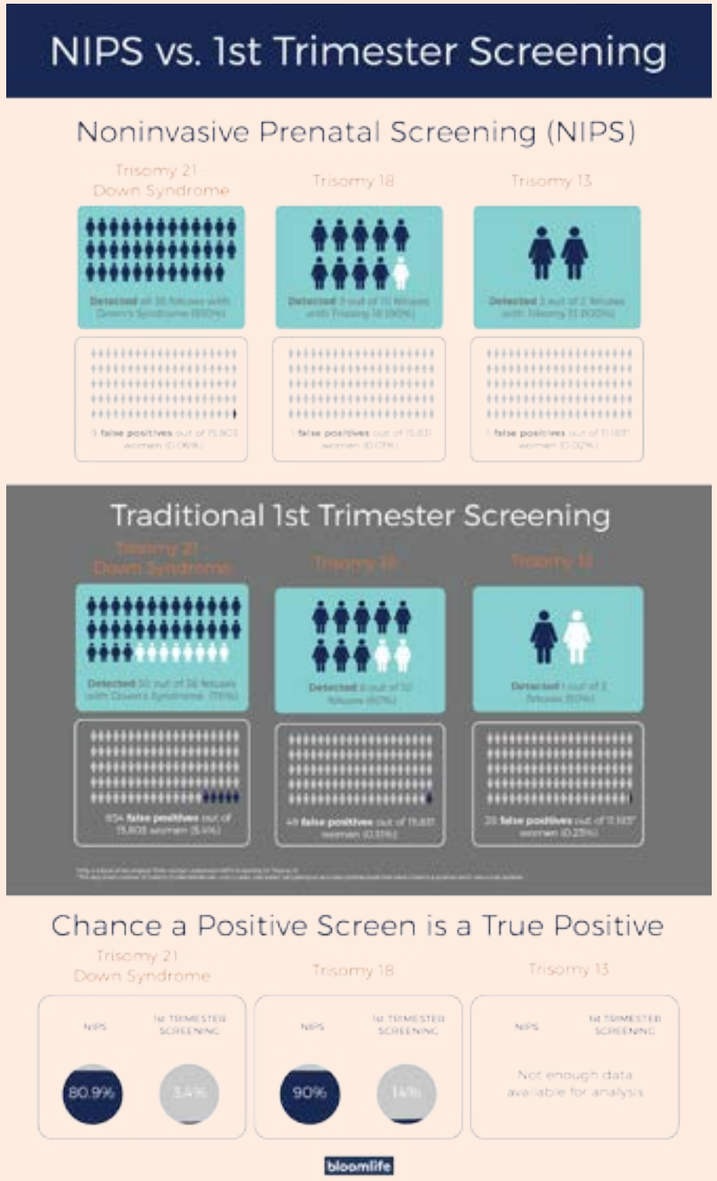
	Age 25	Age 40
Trisomy 21	33%	87%
Trisomy 18	13%	68%
Trisomy 13	9%	57%

SOURCE: ACOG's Committee Opinion: Cell-free DNA Screening for Fetal Aneuploidy

Notably, NIPS is less accurate for other disorders such as trisomies 13 and 18 and the sex chromosomes than it is for Down Syndrome. For these genetic disorders, NIPS detects between 90-98% of affected fetuses, and missed diagnoses occur more frequently.

For all genetic disorders, including Down's, the positive predictive value is far lower than the detection rate. This is because both the false positive rate and the baseline risk affect the positive predictive value, as shown in the infographic below.

Comparing NIPS with traditional screening



Although NIPS is not "99% accurate", NIPS is far more accurate than any of the traditional screens for the three most common trisomies and for the sex chromosome aneuploidies. A positive on a first trimester screen for Down Syndrome, for example, has just a 14% chance of being a true positive. For NIPS, it has a 90% chance of being a true positive.

Special Topics:

Criticisms of NIPS--justified or not?

Since becoming available in 2011, NIPS has been the target of numerous criticisms and controversies some justified, or at least rooted in legitimate concerns, but many not.

LET'S UNPACK THEM ONE AT A TIME:

Criticism #1: Not diagnostic.

Despite being more accurate than traditional blood- and ultrasound-based screens, NIPS is not diagnostic. Only invasive testing (CVS or amnio) will tell you for certain whether your baby has a specific genetic disorder.

Criticism #2: Oversold

(Or, really, misunderstood.)

The rush to integrate NIPS into prenatal screening led to some missteps. A handful of patients were informed, erroneously, that a positive NIPS result was diagnostic of a genetic disorder. Tragically, they then terminated healthy pregnancies.

Some in the press faulted the NIPS companies for these tragedies. This is unfair, in our opinion. The companies have been clear about their tests' performance, but not everyone understood what those numbers really meant or how to translate those numbers into clinical practice.

Regardless, these cases underscore why further testing is warranted after a NIPS positive.

Criticism #3: No calls and indeterminate results.

When the DNA analysis is inconclusive, the test returns a "no-call". Anywhere from 1 to 4% of pregnant women receive no-calls on NIPS. About half of the time, a second blood draw and NIPS test will yield a result.

Certain pregnant women have higher chances of receiving a no-call:

- Roughly 10% of women who weigh over 250 lbs receive no-calls.
- Women carrying a fetus with a genetic defect. In one study, 23% of women who received no-calls carried fetuses with genetic defects. Other studies give lower-- but still elevated above baserate--estimates (around 2.7%).

The American College of Obstetricians and Gynecologists (ACOG) recommends women who receive no-calls be offered additional screening, invasive testing, and genetic counseling.

Criticism #4: May miss rare genetic problems

(Possibly a concern)

The American College of Obstetricians and Gynecologists (ACOG) warns that for women under 35, NIPS misses more genetic abnormalities than traditional screens.

Compared with older women, women under 35 have a lower chances of carrying with a baby with a trisomy or a sex chromosome abnormality--the specific genetic problems NIPS targets.

In contrast, women under 35 do not have a lower risk of carrying a fetus with a rare genetic disorder. The risk of rare genetic disorders--such as microdeletions (tiny missing pieces of chromosomes), mosaicism (in which some cells are chromosomally abnormal and others are not), or triploidy (in which three complete copies of the 23 chromosomes are inherited--typically do not rise substantially with age.

Here's why this matters: Traditional screens, which rely on indirect markers of genetic problems, can be thought of as casting a wide, loose-knit net. Sometimes these markers are found in healthy pregnancies. Sometimes they are absent in affected pregnancies.

These markers also occur with increased frequency in certain rare genetic disorders. Thus, traditional screens also--inadvertently--pick up some rare genetic disorders [13].

In comparison, NIPS is like a fine sieve. It is relies on fetal DNA and is therefore precisely targeted to find specific chromosomal abnormalities. As a result, NIPS is better at catching trisomies but may miss other rare genetic disorders [14].

I say may, because in truth, the science is not in on this question. We do not know whether in practice NIPS misses the rare abnormalities that other screens would have caught.

ACOG lists this missing rare disorders as a concern with NIPS because of statistical estimates, not clinical data. Researchers have looked at disorders detected by screens followed by invasive tests and then modeled--using what I consider overly conservative assumptions--which of these disorders NIPS would have detected [15].

What we can say from these studies is that all screens--NIPS and the traditional screens--miss between 10-25% of all genetic disorders detectable by invasive testing [16].

In short, if you want to detect as many genetic disorders as possible, invasive testing via amnio or CVS remains the definitive option.

Criticism #5: Cost

NIPS costs more than traditional prenatal screenings, including the comprehensive traditional screen, the combined test ($500-2000 versus $150). Some experts have therefore advocated reserving NIPS for high risk women [20].

From a public health and insurance perspective, costs considerations are inevitable, real, and important.

But we mislead millions of women when we label such efforts as “recommendations”. The label “recommendations” implies that these guidelines were designed to maximize women’s personal preferences, or to minimize their chances of having a baby with a genetic disorder rather than to reduce costs.

Criticism #6: Lack of Data

(Formerly a Concern).

When NIPS first hit the market in 2011, all the clinical data on their performance came from studies involving women over 35 . [21]

There was no reason to expect that NIPS would be less accurate in low risk women. But studies of younger women-who as a group are less prone to trisomies--were prohibitively expensive for the fledgling companies. Studies of younger women would require tens of thousands of patients to achieve adequate statistical power.

Since 2011, however, researchers have tracked NIPS performance in several large post-market studies involving over 100,000 low-risk women. These studies confirm what we expected: NIPS performs similarly well among low-risk women and high risk women, and is better than traditional screens at detecting the three most common trisomies and sex chromosome aneuploidies [22].

Special Topics:

NIPS after a Positive Traditional Screen

NIPS is sometimes offered as an alternative to invasive testing after a woman receives a positive on a traditional screen [17].

Because NIPS is not designed to detect most rare genetic disorders, this practice substantially increases your odds of a missed diagnosis. For women with a positive screen, around 2-3% will have a diagnosis invasive testing would uncover but NIPS would miss [18]. For women with a structural abnormality found on ultrasound, this percentage rises to between 6 and 8%.

Additional citations:

[19] http://www.ncbi.nlm.nih.gov/pubmed/24861197

[17] http://www.ncbi.nlm.nih.gov/pubmed/23635685

Special Topics:

Choosing the Right NIPS test for You

In the U.S., four companies provide the majority of NIPS testing:

- Harmony™ by Ariosa (acquired by Roche in 2015)
- MaterniT21™ by Sequenom
- Verifi™ by Illumina
- Panorama™ by Natera

Each of these companies uses a slightly different approach to analyzing cell-free DNA. These differences are highly technical, something mainly of concern to biologists and statisticians, not patients.

But some differences between NIPS providers, however, do affect patients.

No-call rate

• When the DNA analysis cannot adequately determine whether the result is positive or a negative,a “no-call” results. Between 1% and 4% of women will receive a no call after a NIPS screen. After a no-call, a second blood draw and analysis yields a result around half of the time.

• Verifi™ has substantially lower rate of no-calls than other noninvasive prenatal screens (0.1% versus 1-4%). About 10% of women weighing over 250 lbs. will receive a no-call. If you weigh over 250 lbs., you may want to use Verifi™ as opposed to other NIPS tests.

• Panorama™ factors the amount of fetal versus maternal cell-free DNA in the mother’s blood into its risk estimate, and will return a no-call if the amount of fetal DNA relative to maternal DNA is too low. Panorama™ is the only NIPS test to include this comparison. As a result, Panorama™ has relatively high rate of no-calls (about 4%) but a lower chance of a missed diagnosis (a false negative) than other NIPS tests.

Screening

• Screening for additional rare genetic abnormalities. All available NIPS tests screen for the three most common trisomies (21, 18, & 13), and sex chromosome aneuploidies if requested. Certains tests also cover select rare genetic disorders.

• Panorama™ screens for triploidy and five of the most common microdeletion syndromes: DiGeorge Syndrome, (DiGeorge), 5p (Cri-du-chat syndrome), 15q (Prader-Willi/Angelman syndromes), 1p36 deletion syndrome, 4p (Wolf-Hirschhorn syndrome).

• These syndromes are caused by a missing piece of a chromosome and lead to moderate to severe mental and physical defects. They are all very rare: Triploidy occurs in 1 in 10,000 births. Each of these microdeletion syndromes occur in between 1 in 2,000 and 1 in 50,000 live births.

• MaterniT21™ screens for the same five microdeletions syndromes as Panorama™, plus two additional microdeletion syndromes (8q, Langer-Giedion syndrome and 11q, Jacobsen syndrome) and two rare trisomies (Trisomy 16 and Trisomy 22). Unlike the Panorama™ test, it does not screen for triploidy.

• ACOG warns against NIPS testing for microdeletions, because they are extremely rare. (Each microdeletions affects somewhere between 1 in 2,000 to 1 in 60,000 live births.) False positives are likely, even with highly accurate tests. Around 95% of positives for these microdeletion syndromes will turn out to be false positives.

Invasive Tests:

6

(Amniocentesis and Chorionic Villus Sampling)

Invasive Tests:

Overview

Chorionic villus sampling (CVS) and amniocentesis (amnio) are the most common invasive tests. They are called invasive because they require extracting fetal cells with a needle from the placenta (CVS) or from the amniotic fluid (amnio).

Invasive tests have two big advantages over screens:

• They are diagnostic. Amnio and CVS are over 99% accurate. They can tell you for certain whether your baby has a particular genetic disorder. By contrast, screens only provide a risk estimate of how likely your baby is to have a genetic problem.

• They cover more ground. Amnio and CVS test for a larger number of genetic abnormalities than screens. Amnio and CVS can detect mosaicism (a mixture of chromosomally normal and abnormal cells), and problems involving tiny pieces of individual chromosomes: like deletions, inversions (a piece of a chromosome gets flipped from its normal position), and translocations (a piece of a chromosome is moved from one location to another). Amnio and CAV also detect certain single-gene disorders like cystic fibrosis and hemophilia. Screens, on the other hand, focus on the three most common trisomies (21,18, and 13) and sex chromosome abnormalities.

Amniocentesis is 100% accurate, while CVS is nearly 100% accurate--the exception being a chromosomal mosaic result on CVS, which occurs in about 1 in 100 CVS tests and requires confirmation by amniocentesis [23]. Around 80% of these mosaic results turn out to be confined to the placenta--meaning the fetus is genetically normal, but its placenta contains a mix of trisomic and normal cells [23].

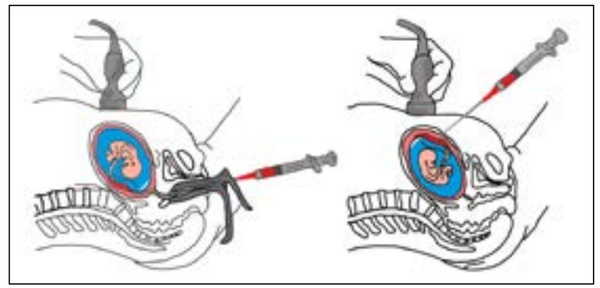
Chorionic Villus Sampling (CVS): The details

Doctors usually perform CVS between 10 and 13 weeks of pregnancy. During CVS, a doctor inserts a needle to extract cells from the placental “villi”.

The position of the placenta determines where the doctor will insert the needle. An ultrasound is used to guide the needle and avoid contact with your baby.

Women sometimes experience pressure, pinching, or mild pain during CVS.

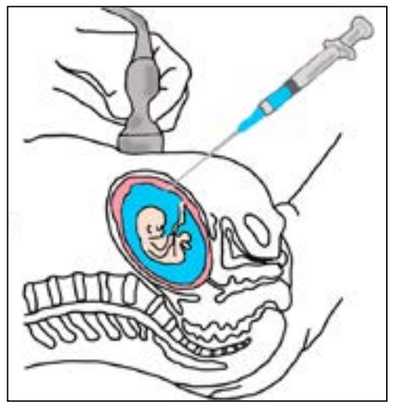
Your doctor will then send the placental cells to a laboratory to be analyzed for common genetic abnormalities.
Results usually return around a week after extraction.



Amniocentesis: The details

During amniocentesis, a doctor will insert a needle through the abdomen and extract a small amount of amniotic fluid. Your doctor will use an ultrasound to guide the needle and avoid contact with your baby. Women sometimes feel pressure, pinching, or mild pain during amniocentesis.

Your doctor will send the amniotic fluid sample to a laboratory, where fetal cells contained in the fluid will be analyzed for genetic abnormalities.



CVS versus amniocentesis:

What are the pros and cons of amnio versus CVS?

CVS's main advantage is that it is performed earlier, between 10 to 13 weeks, allowing for decision making while still in your first trimester, before you begin to show and before many of your friends and family may be aware of your pregnancy. By contrast, amniocentesis cannot safely be performed until 15 to 20 weeks.

Amnio's main advantage is that in additional to testing for genetic disorders, it also tests for spina bifida, a congenital defect caused by failure of the neural tube to close completely early in pregnancy (between 21 and 28 days after conception). Spina bifida occurs in about 1 in 1000 births worldwide. In the U.S., the rate is lower, 2 to 4 out of every 10,000 births.

Women who undergo CVS will still need a second trimester alpha fetoprotein (AFP) test for spina bifida.This AFP test requires only a simple blood draw. The AFP test is most accurate between 16-18 weeks, and so stretches out the waiting game into the second trimester.

The second trimester anatomy ultrasound--recommended regardless of what screen or invasive test you choose and typically done between 18 and 20 weeks--can also detect some cases of spina bifida.

Special Topics:

Invasive Tests – Only for Woman Over 35?

From the 1970s until the 2000s, amniocentesis (amnio) and chorionic villi sampling (CVS), collectively known as invasive tests, were only offered to high-risk women (women over 35 or who had a family or personal history of genetic disorders).

Since 2007, however, all major medical organizations, including the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Geneticists (ACMG) recommend offering invasive tests to all women, regardless of their age.

When CVS and amnio were first introduced, they were expensive. Major medical organizations therefore recommended restricting testing to high risk pregnant women to keep costs down.

As the technology used to analyze DNA has improved, however, these costs dropped considerably and are no longer a consideration.

The other drawback to CVS and amnio is an increased risk of miscarriage. Prior to 2007, ACOG and other medical organizations stated that the chance of miscarriage was unacceptably high for women at low risk of carrying a child with a genetic disorder.

Blanket recommendations like these meant women themselves had little say in whether they received these tests, given how they personally weighed the risk of miscarriage against the risk of having a child with a genetic disorder.

Now, though, women can decide for themselves whether to undergo invasive testing. And this increased choice makes it especially important that women have access to sound information about invasive tests, including the data around the chances of miscarriage (covered in the next section.)

Special Topics:

How Often Do Invasive Tests Cause Miscarriage?

(The risk is lower than you might think.)

Statistics on how much invasive testing raises the risk of a miscarriage range widely. The Centers for Disease (CDC), for instance, states the increased risk as 1 in 100 to 1 in 200 for CVS, and 1 in 200 to 1 in 400 for amniocentesis. The American College of Obstetricians (ACOG) places the risk lower, stating it for both amnio and CVS as 1 in 350 to 1 in 500, while noting that with an experienced provider the risk is likely even lower. Emily Oster in her bestselling book Expecting Better claims based on her review of the evidence that the risk is the same for CVS and amnio, around 1 in 800. And a large prospective study done in Denmark of over 140,000 pregnancies found no increase at all [24].

This disagreement is frustrating, because these numbers matter. For example, I would personally find a 1 in 50 risk of miscarriage unacceptably high. I would only take such a risk if I had already received a positive on a prenatal screen. But I consider a 1 in 500 risk acceptably low--a chance I would willingly take in exchange for the extra accuracy and breadth of an invasive test.

Fortunately for those considering amnio or CVS, the current evidence strongly favors the lower estimates.

The higher (1 in 50, 1 in 100) estimates rely on older data. The 1 in 100 estimate, for example, comes from a randomized controlled trial (the gold standard for medical studies) conducted in the 1980s [25], before routine ultrasound guidance of these procedures. Ultrasound guidance helps doctors avoid fetal contact and the need for repeated needle insertions, dramatically lowering the risk of miscarriage.

Sources continue to cite this randomized trial simply because it's the only one. No randomized controlled trials on amnio (or CVS) have been conducted since.

Thus, to determine the risk of miscarriage using modern CVS and amnio techniques, we must rely on observational studies, in which researchers compare the miscarriage rates of women who undergo amnio and CVS with those who do not undergo these procedures.

On the whole, these observational studies are reassuring. A meta-analysis of such studies published since 2000 found that the increased risk of miscarriage was tiny--about 1 in 1000 for amnio and about 1 in 500 for CVS. The increase in risk was so slight in fact that it failed to reach statistical significance, meaning it may have occurred by chance alone [26].

But even these low estimates likely overstate the true risk.

Why? The studies look at how many women lost a baby after an invasive test, rather than how many *more* woman lost a baby after an invasive test. Not all miscarriages that occur after an invasive procedure result directly from the procedure. Some of them would have happened even without invasive testing.

Here's what we actually need to know: How much do invasive tests increase the chances of miscarriage above the expected number of miscarriages?

This is a tough question, because determining the expected number of miscarriage is far from simple. Older women, for instance, have a higher rate of miscarriage than younger women, well into the second trimester [27]. Fetuses with abnormal screening results are miscarried at a higher rate than those with normal results [28]. Older fathers have a higher miscarriage rate than younger fathers. And duration of pregnancy also matters: The chances of miscarriage diminish with each passing week.

In an ideal world, researchers would compare miscarriage among women undergoing CVS and amnio with women matched by all these factors. But most observational studies fall short on this account. Most studies simply compare women who receive invasive testing with all other pregnant women, matched only by gestational age. The failure to consider other risk factors inflates the apparent increase in the risk of miscarriage.

Case in point: in the handful observational studies that other risk factors into account, women undergoing invasive testing do not have a higher risk of miscarriage than women who do not undergo invasive testing. [29]

The Bottom Line

For those considering CVS or amnio, take heart. The miscarriage risk is almost certainly far lower than commonly stated, somewhere in the neighborhood of 1 in 500 to 1 in 1000.

If you do decide to undergo amnio or CVS, look for an experienced provider--someone who performs these procedures several times a day. These providers have the best track records and, as ACOG notes, the lowest risk of complications.

7

Genetic Abnormalities:

(a quick primer)

Genetic Abnormalities: A quick primer

Now that you've made it through most of the e-book (or perhaps you skipped ahead to figure out what the heck we are talking about with all of these genetic disorders), we're going to elaborate on what disorders these prenatal screens and tests detect.

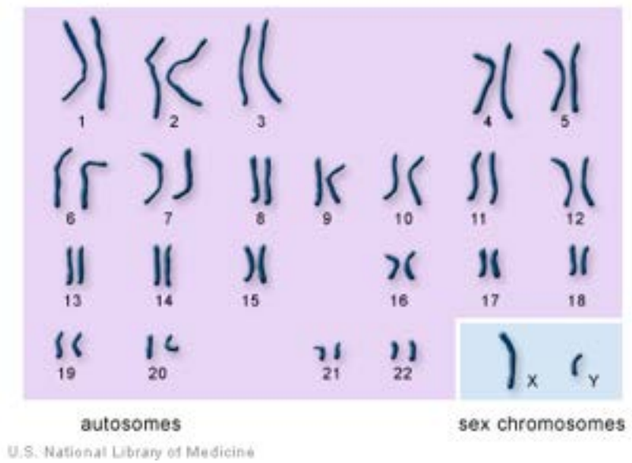
Aneuploidy -- Monosomies and Trisomies

For all of us whose last biology class was ages ago, a quick Bio 101 refresher, :

Every cell in our body contains DNA, the genetic blueprint for building and maintaining a human.

This DNA is coiled and wrapped and packaged into chromosomes, like yarn wound into a ball. The DNA is divided up into 23 pairs of chromosomes (46 total), half originating from our mother and half from our father.

If you're a man, your 23 chromosome pairs look like this:



U.S. National Library of Medicine

If you're a women, your complement of chromosomes looks the same, except you carry two X sex chromosomes rather than an X and a Y.

One of chromosome's key functions is helping our cells correctly copy and apportion DNA when cells divide.

In preparation for fertilization, precursor cells divide multiple times to become the egg and sperm.

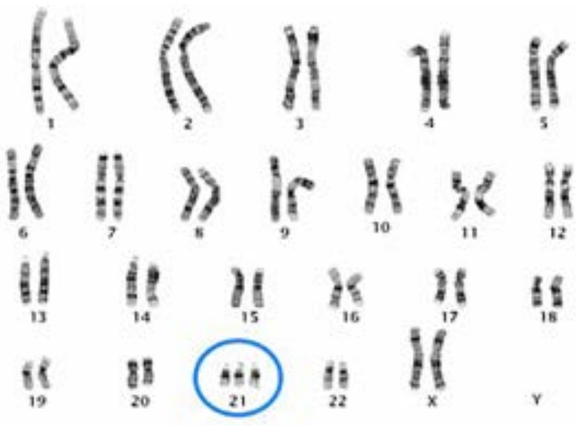
Sometimes these early divisions go awry, with the chromosomes failing to distribute evenly between the two new daughter cells.

For example, an egg can end up 24 chromosomes (instead of the normal 23). When fertilized, this egg develops into a fetus that carries an extra chromosome-- for a total 47 rather than 46 chromosomes.

When an incorrect number of chromosomes occurs--this is called aneuploidy. A single extra chromosome is called a trisomy, because one of the chromosomes pairs has an extra partner, a set of three instead of two.

Down Syndrome is the most well known and common type of trisomy. Down Syndrome accounts for a staggering 50% of all genetic disorders detected by prenatal testing [30].

Down Syndrome is caused by an extra copy of chromosome 21. People with Down Syndrome have three copies of chromosome 21 instead of two.



Trisomies

After Down Syndrome, Edward's Syndrome (an extra chromosome 18) and Patau's Syndrome (an extra chromosome 13) are the most common types of trisomy. Together these three trisomies make up about 75% of all genetic abnormalities detected prenatally [31] [30]

These trisomies are relatively common because they are less deleterious than other chromosomal errors. Trisomies involving other chromosomes can occur, but most are not viable--they either fail to implant into the lining of the uterus after fertilization or are lost early in pregnancy.
While Down Syndrome and Trisomies 13 and 18 do result in live births, they too are often not viable. Around 40-50% of fetuses with Down Syndrome are lost before delivery, with about 30% of these losses happening after 10 weeks

[32]. Trisomy 13 and 18 pregnancies are lost at even greater rates: About 70-80% of affected pregnancies will be lost before birth [33].

Sex Chromosome Aneuploidies

The next most common aneuploidies involve the so-called sex chromosomes (X and Y) that determine biological sex. Sex chromosome aneuploidies make up between 8-10% of all genetic abnormalities detected prenatally [30][19].

Most men carry an X and a Y, and most women carry two Xs. But not all men and women.

Sometimes a person carries an extra sex chromosome, as in XXX or Triple X Syndrome. Sometimes a person is missing a sex chromosome, as in X0 or Turner Syndrome. Men sometimes carry an extra Y or an extra X chromosome. The latter condition, denoted XXY, leads to Klinefelter Syndrome.

Unlike Down Syndrome and Trisomy 13 and 18, most sex chromosome aneuploidies cause no or only mild cognitive and physical defects. They do, however, often lead to infertility.

Structural Problems

Aneuploidies, which involve whole extra or missing chromosomes, are not the only common type of chromosomal disorders. Sometimes during early egg and sperm cell divisions, small mistakes are made in the copying of the chromosomes. Tiny pieces of a single chromosome can fail to be copied (deletions), can be copied more than once (duplications), and can get moved from one place to another (translocations).

Collectively these chromosomal disorders are known as structural problems, because they affect the structure of a single chromosome.

Most structural problems occur at random, meaning that--unlike with aneuploidies--the risk for does not rise with yours or your partner's age. The risk of any structural problem is about 1 in 100.

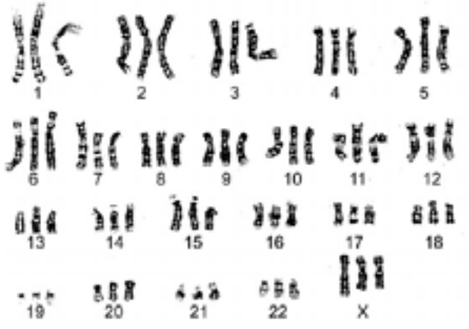
Triploidy

Triploidy occurs when a fetus inherits a full extra set of chromosomes. The fetus then has three copies of each chromosome instead of two, for a total 69 chromosomes instead of the normal 46.

Triploidy is caused by improper early divisions of the egg or sperm before fertilization. It can also be caused by two sperm fertilizing the egg at the same time.

Triploidy occurs at random. Your chances of triploidy do not increase with you or your partner's age.

Scientists believe that triploidy may be surprisingly common, perhaps affecting up to 1-2% of all conceptions. Nearly all of these conceptions are lost early in pregnancy. Only 1 in 10,000 make it to delivery. Affected babies who make it to birth nearly always pass away within 10 months [33].



Mosaicism

Sometimes a fetus contains a mix of chromosomally normal and chromosomally abnormal cells, This is known as mosaicism.

Aberrant cell divisions that occur shortly after conception can lead to mosaicism. An early copying error is propagated in all subsequent divisions within a cell line, resulting in chromosomal abnormalities in some but not all of the baby's cells.

Other times mosaicism is caused by the opposite: The baby starts out with an abnormal number of chromosomes, but a subset of early cells undergo "rescue" divisions, reverting back to a normal number of chromosomes. Depend-

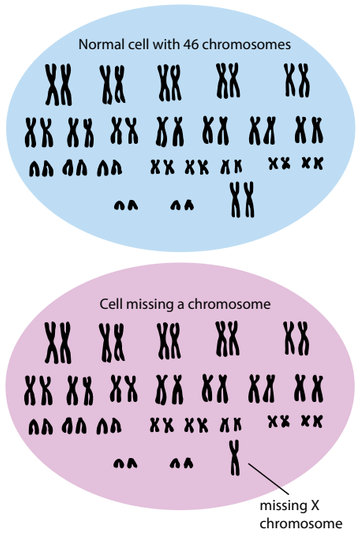
ing on exactly when these early abnormal cell divisions occur, mosaicism can affect the fetus, the placenta, or both the fetus and the placenta.

Mosaicism found only in the placenta is called confined placental mosaicism (CPM). CPM is surprisingly common, affecting an estimated 1% of all fetuses [34], and occurs far more often than mosaicism that affects the fetus. Because the fetus is chromosomally normal, most pregnancies with CPM progress normally. Around 20% of the time, however, CPM affects fetal growth, causing intrauterine growth restriction.

What CPM most often causes problems for is prenatal genetic testing. CMP can result in false positives on chorionic villus sampling (CVS) and non-invasive prenatal screening (NIPS), because these tests use placental--not fetal--DNA to screen for genetic disorders.

(Around 8 out of 10 mosaic results on CVS turn out to be confined to the placenta. Selection is the likely reason: fetuses affected by mosaicism are frequently lost during early pregnancy. Fetuses whose mosaicism is confined to their placentas, on the other hand, have higher odds of survival. Any mosaic result on CVS should be confirmed with direct examination of fetal DNA via amniocentesis.)

True fetal mosaicism can cause a large range of clinical outcomes, depending on the chromosomal abnormality involved and which specific cells are affected.




Chromosomal Mosaicism

Any mosaic result on CVS should be confirmed with direct examination of fetal DNA via amniocentesis.)

True fetal mosaicism can cause a large range of clinical outcomes, depending on the chromosomal abnormality involved and which specific cells are affected.

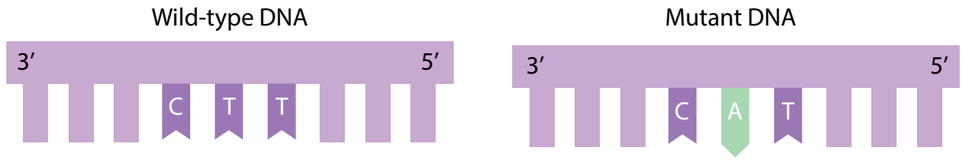
Single Gene Mutations

Another set of genetic problems (why are there so many?) stem from alterations within a single gene.

We carry two copies of our chromosomes--except in the case of the X and Y chromosomes for men--so we typically inherit two copies of most genes.

Sometimes inheriting just one mutated copy can cause a genetic disorder--as in the most common form of dwarfism, achondroplasia. Such mutations are called dominant, because the effect of the mutated gene dominates over the effect of the normal copy.

Other times we have to inherit the same mutation from both parents to have a disorder, as in the most common mutation causing cystic fibrosis. Such mutations are called recessive, because they cause harm only when two defective copies are present.



Single gene mutation

8

Figuring Out Your Personal Risk

Figuring Out Your Personal Risk:

Maternal Age

A woman's age is the biggest risk factor for aneuploidy--a baby that carries an abnormal number of chromosomes. Down's Syndrome, Edward's Syndrome, and Turner's Syndrome are all types of aneuploidy.

The risk for aneuploidy rises slowly throughout a woman's 20s, faster during her 30s, and then very rapidly in her 40s.

That's the bad news.

The good news is that even well into your mid-40s, the odds favor you carrying a healthy baby. Plus, a woman's age mostly increases her risk of aneuploidies; it does not raise her risk for most other types of chromosomal abnormalities. In fact, when you look at birth defects as a whole, as opposed to just chromosomal abnormalities, older women are at lower overall risk than younger women [35].

Maternal Age and the Risk of Trisomy

Prenatal genetic testing began as a way to detect Down Syndrome, the most common genetic disorder. The risk of Down Syndrome rises steeply with age.

On the next page is your risk of having a child with Down Syndrome by mother's age. The data are from all births in England between the years of 1989 and 1998.

This table also includes your risk of having a child with any aneuploidy (any missing or extra chromosome, including Down Syndrome) based on your age. As with Down Syndrome, the risk of any aneuploidy rises steeply with age.

Age of Mother	Risk of Down Syndrome	Risk of Aneuploidy--Any MIssing or Extra Chromosome
20	1 in 1667	1 in 526
21	1 in 1667	1 in 526
22	1 in 1429	1 in 500
23	1 in 1429	1 in 500
24	1 in 1250	1 in 476
25	1 in 1250	1 in 476
26	1 in 1176	1 in 476
27	1 in 1111	1 in 455
28	1 in 1053	1 in 435
29	1 in 1000	1 in 417
30	1 in 952	1 in 384
31	1 in 909	1 in 384
32	1 in 769	1 in 323
33	1 in 625	1 in 286
34	1 in 500	1 in 238
35	1 in 385	1 in 192
36	1 in 294	1 in 156
37	1 in 227	1 in 127
38	1 in 175	1 in 102
39	1 in 137	1 in 83
40	1 in 106	1 in 66
41	1 in 82	1 in 53
42	1 in 64	1 in 42
43	1 in 50	1 in 33
44	1 in 38	1 in 26
45	1 in 30	1 in 21
46	1 in 23	1 in 16
47	1 in 18	1 in 13
48	1 in 14	1 in 10
49	1 in 11	1 in 8

Source: https://embryology.med.unsw.edu.au/embryology/index.php/Genetic_risk_maternal_age

(The above table refers to the chance of giving birth to a child with Down Syndrome, not the chance of carrying a child with Down Syndrome. The risk of Down Syndrome during pregnancy is higher than the risk of Down Syndrome at birth, because approximately 30-40% of Down Syndrome pregnancies are lost after the first trimester [32])

Father's Age and the Risk of Aneuploidy

The father's age does not affect the risk of aneuploidy. Approximately 90% of the genetic errors that cause trisomy come from the egg. Only about 10% come from the sperm and these occur at random.

Other Risk Factors for Aneuploidy

If you have carried a baby with Down Syndrome before, your risk of carrying another baby with Down Syndrome is about 2.5 times higher than than what it would be based on your age alone. You also have about a 60% higher chance of carrying a baby with another trisomy [36].

In relative terms, these numbers are scary. But in absolute terms, they are far less so. Only a small number of women with a prior affected pregnancy actually go on to have another affected pregnancy. In a large Australian-based study, only 2% of women who previously carried a baby with a trisomy were diagnosed with a trisomy in a subsequent pregnancy [37].

There is one rare exception: A small percentage of women or their partners who have previously had a fetus with Down Syndrome themselves carry a chromosomal abnormality called a balanced Robertsonian Translocation. People with a balanced Robertsonian Translocation have a normal number of chromosomes, but one of their copies of chromosome 21 has fused to different chromosome--often to chromosome 14. Female carriers have a 12% chance of carrying another baby with Down Syndrome. If their partner has the translocation, the chance is 3%. You can have genetic testing done to determine if you or your partner carry a balanced Robertsonian Translocation.

Other Chromosomal Abnormalities

Trisomies and other aneuploidies are not the only chromosomal abnormalities to consider when choosing a prenatal test. Structural abnormalities, which occur when tiny pieces of single chromosomes are deleted, flipped, or moved during early development, can also cause lifelong mental and physical disability.

Individually, structural abnormalities are very rare, far less common than Down Syndrome, for instance. Collectively, though, structural abnormalities occur in about 1 in 100 pregnancies.

Unlike for Down Syndrome and other aneuploidies, a woman's age does not affect her risk. In practice, this means the risk of a structural abnormality is higher than the risk of aneuploidy until age 38. A 30-year-old woman's risk of carrying a baby with a structural abnormality, for example, is 4 times greater than her risk of carrying a baby with Down Syndrome [18].

This matters for choosing a prenatal test: Screens were not designed to detect structural abnormalities. They can only detect a small fraction of these disorders. Amnio and CVS, on the other hand, can detect nearly all of them.

In short, if you want comprehensive testing, consider skipping the screens and undergoing either amnio or CVS.

Conclusion

Conclusion:

You've reached the end! If you came searching for a right or wrong answer, our apologies, you won't find it here. We wrote this ebook to provide an in-depth resource with scientific, evidence-based backing, to give *you* the power to answer these big questions for yourself, as a parent.

Prenatal genetic testing, like so many pregnancy and parenting decisions, comes down to personal preferences. The benefits and risks of your options have to be weighed in the context of your life and beliefs.

Consider yourself armed with information. There are no right or wrong answers.

You are clearly going to be a thoughtful and amazing parent. Congratulations!

About the Authors:

Amy Kiefer

A researcher by training, Amy hold a Ph.D. in Psychology and an M.A. in Statistics. She lives in the Bay Area with her husband and two children where she blogs about fertility, pregnancy, and breastfeeding. Follow her @xpectingscience on Twitter or like Expecting Science on Facebook for more evidence-based parenting information.

Molly Dickens

Molly heads up Content and Community at Bloomlife. She holds her PhD in Physiology and, in her days as an academic research scientist, studied stress and fertility. She is generally fascinated by all things related to growing tiny humans and thinks all women should have better information to feel confident in their decisions during pregnancy.

About Bloomlife:

Bloomlife is a women's health company focused on providing expecting moms with better information to have a simplified and smarter pregnancy. With their first product, Bloomlife is introducing the world's first clinically validated smart pregnancy tracker that automatically tracks and counts contractions.

The Bloomlife pregnancy tracker is a trusted second opinion, helping expecting moms understand her body by providing a better way to learn about and track contractions and have quality information at her fingertips.

For more information about Bloomlife, visit our website:
www.bloomlife.com

REFERENCES

1. Snijders R, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Lancet. 1998;352: 343–346.
2. Wald NJ, George L, Smith D, Densem JW, Pettersonm K, on behalf of the International Prenatal Screening Research Group**. Serum screening for Down's syndrome between 8 and 14 weeks of pregnancy. BJOG. 1996;103: 407–412.
3. Serum screening for Down's syndrome between 8 and 14 weeks of pregnancy. International Journal of Gynecology & Obstetrics. 1996;55: 193.
4. Stenhouse EJ, Crossley JA, Aitken DA, Brogan K, Cameron AD, Connor JM. First-trimester combined ultrasound and biochemical screening for Down syndrome in routine clinical practice. Prenat Diagn. 2004;24: 774–780.
5. O'Leary P, Breheny N, Dickinson JE, Bower C, Goldblatt J, Hewitt B, et al. First-trimester combined screening for Down syndrome and other fetal anomalies. Obstet Gynecol. 2006;107: 869–876.
6. Benn P, Norwitz ER, Pergament E. Cell-free DNA vs sequential screening for the detection of fetal chromosomal abnormalities. Am J Obstet Gynecol. 2016;215: 252–253.
7. Lau GW, Feldman DS, Morales CM, Smith D, Edwards R, Williams J 3rd. First-trimester aneuploidy screening: is there a maternal age at which it loses effectiveness? J Reprod Med. 2014;59: 443–447.
8. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med. 2005;353: 2001–2011.
9. Pergament E, Cuckle H, Zimmermann B, Banjevic M, Sigurjonsson S, Ryan A, et al. Single-Nucleotide Polymorphism–Based Noninvasive Prenatal Screening in a High-Risk and Low-Risk Cohort. Obstetrics & Gynecology. 2014;124: 210–218.
10. Yaron Y, Jani J, Schmid M, Oepkes D. Current Status of Testing for Microdeletion Syndromes and Rare Autosomal Trisomies Using Cell-Free DNA Technology. Obstet Gynecol. 2015;126: 1095–1099.
11. Meck JM, Kramer Dugan E, Matyakhina L, Aviram A, Trunca C, Pineda-Alvarez D, et al. Noninvasive prenatal screening for aneuploidy: positive predictive values based on cytogenetic findings. Am J Obstet Gynecol. 2015;213: 214.e1–5.
12. Hochstenbach R, Page-Christiaens GCML, van Oppen ACC, Lichtenbelt KD, van Harssel JJT, Brouwer T, et al. Unexplained False Negative Results in Noninvasive Prenatal Testing: Two Cases Involving Trisomies 13 and 18. Case Rep Genet. 2015;2015: 926545.
13. Tørring N, Petersen OB, Becher N, Vogel I, Uldbjerg N, Danish Fetal Medicine Study Group, et al. First trimester screening for other trisomies than trisomy 21, 18, and 13. Prenat Diagn. 2015;35: 612–619.
14. Norton ME, Jelliffe-Pawlowski LL, Currier RJ. Chromosome abnormalities detected by current prenatal screening and noninvasive prenatal testing. Obstet Gynecol. 2014;124: 979–986.
15. Lebo RV, Novak RW, Wolfe K, Michelson M, Robinson H, Mancuso MS. Discordant circulating fetal DNA and subsequent cytogenetics reveal false negative, placental mosaic, and fetal mosaic cfDNA genotypes. J Transl Med. 2015;13: 260.
16. Syngelaki A, Pergament E, Homfray T, Akolekar R, Nicolaides KH. Replacing the combined test by cell-free DNA testing in screening for trisomies 21, 18 and 13: impact on the diagnosis of other chromosomal abnormalities. Fetal Diagn Ther. 2014;35: 174–184.
17. Norton ME, Rose NC, Benn P. Noninvasive prenatal testing for fetal aneuploidy: clinical assessment and a plea for restraint. Obstetrics & Gynecology. 2013;121: 847–850.
18. Evans MI, Wapner RJ, Berkowitz RL. Noninvasive prenatal screening or advanced diagnostic testing: caveat emptor. Am J Obstet Gynecol. 2016;215: 298–305.
19. Davis C, Cuckle H, Yaron Y. Screening for Down syndrome - incidental diagnosis of other aneuploidies. Prenat Diagn. 2014;34: 1044–1048.
20. Morris S, Karlsen S, Chung N, Hill M, Chitty LS. Model-based analysis of costs and outcomes of non-invasive prenatal testing for Down's syndrome using cell free fetal DNA in the UK National Health Service. PLoS One. 2014;9: e93559.
21. Macones GA. Helping providers interpret cell-free fetal DNA testing. Am J Obstet Gynecol. 2015;213: 2.
22. Taneja PA, Snyder HL, de Feo E, Kruglyak KM, Halks-Miller M, Curnow KJ, et al. Noninvasive prenatal testing in the general obstetric population: clinical performance and counseling considerations in over 85 000 cases. Prenat Diagn. 2016;36: 237–243.
23. Schreck RR, Falik-Borenstein Z, Hirata G. Chromosomal mosaicism in chorionic villus sampling. Clin Perinatol. 1990;17: 867–888.
24. Wulff CB, Gerds TA, Rode L, Ekelund CK, Petersen OB, Tabor A, et al. Risk of fetal loss associated with invasive testing following combined first-trimester screening for Down syndrome: a national cohort of 147 987 singleton pregnancies. Ultrasound Obstet Gynecol. 2016;47: 38–44.
25. Tabor A, Philip J, Madsen M, Bang J, Obel EB, Nørgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet. 1986;1: 1287–1293.
26. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;45: 16–26.
27. Cohen-Overbeek TE, Hop WC, den Ouden M, Pijpers L, Jahoda MG, Wladimiroff JW. Spontaneous abortion rate and advanced maternal age: consequences for prenatal diagnosis. Lancet. 1990;336: 27–29.
28. Akolekar R, Bower S, Flack N, Bilardo CM, Nicolaides KH. Prediction of miscarriage and stillbirth at 11-13 weeks and the contribution of chorionic villus sampling. Prenat Diagn. 2011;31: 38–45.
29. Ogilvie C, Akolekar R. Pregnancy Loss Following Amniocentesis or CVS Sampling-Time for a Reassessment of Risk. J Clin Med Res. 2014;3: 741–746.
30. Wellesley D, Dolk H, Boyd PA, Greenlees R, Haeusler M, Nelen V, et al. Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe. Eur J Hum Genet. 2012;20: 521–526.
31. Alamillo CML, Krantz D, Evans M, Fiddler M, Pergament E. Nearly a third of abnormalities found after first-trimester screening are different than expected: 10-year experience from a single center. Prenat Diagn. 2013;33: 251–256.
32. Snijders RJ, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age- and gestation-specific risk for trisomy 21. Ultrasound Obstet Gynecol. 1999;13: 167–170.
33. Lakovschek IC, Streubel B, Ulm B. Natural outcome of trisomy 13, trisomy 18, and triploidy after prenatal diagnosis. Am J Med Genet A. 2011;155A: 2626–2633.
34. Kalousek DK, Vekemans M. Confined placental mosaicism. J Med Genet. 1996;33: 529–533.
35. Goetzinger KR, Shanks AL, Odibo AO, Macones GA, Cahill AG. Advanced Maternal Age and the Risk of Major Congenital Anomalies. Am J Perinatol. 2016; doi:10.1055/s-0036-1585410
36. Warburton D, Dallaire L, Thangavelu M, Ross L, Levin B, Kline J. Trisomy recurrence: a reconsideration based on North American data. Am J Hum Genet. 2004;75: 376–385.
37. De Souza E, Halliday J, Chan A, Bower C, Morris JK. Recurrence risks for trisomies 13, 18, and 21. Am J Med Genet A. 2009;149A: 2716–2722.

bloomlife