



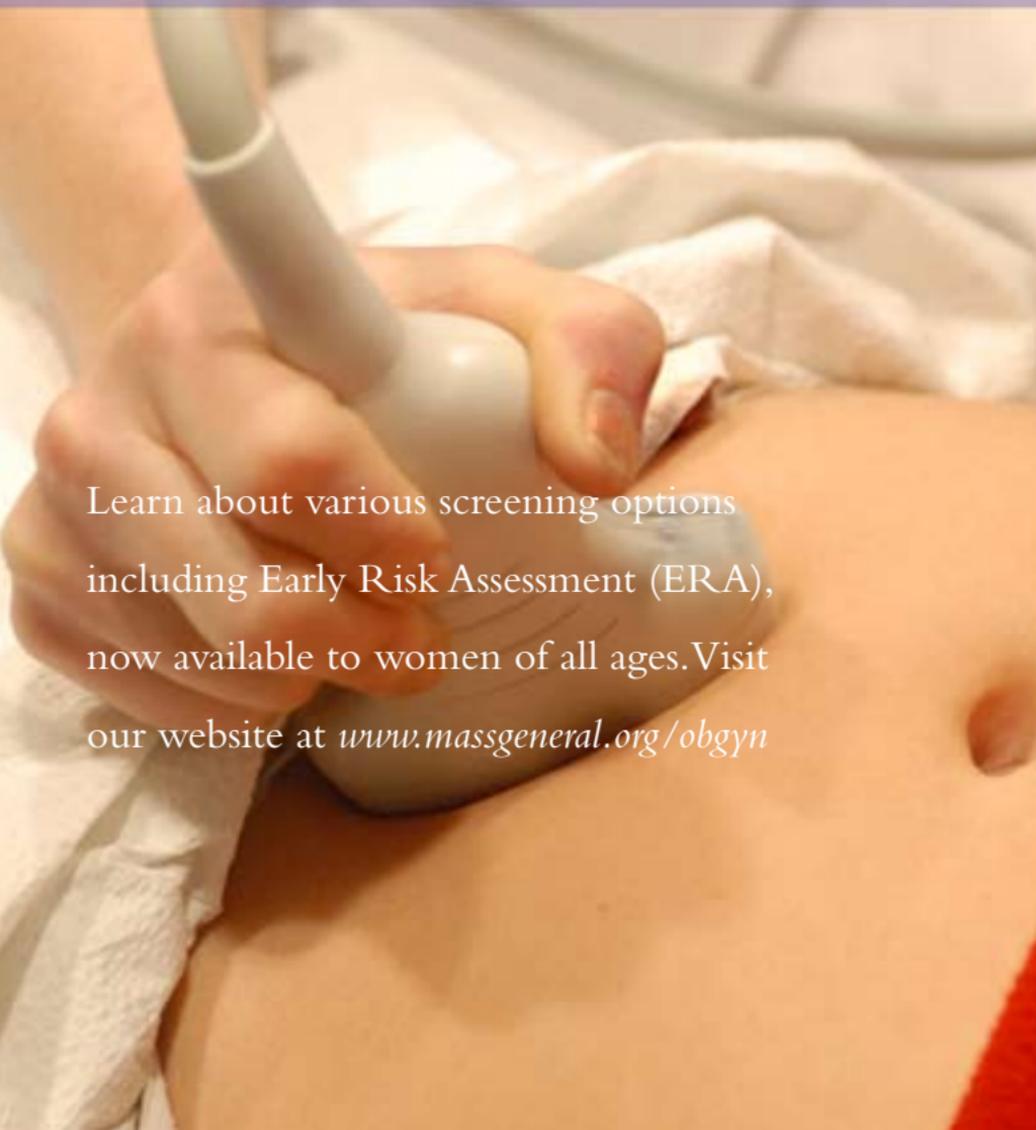
MASSACHUSETTS
GENERAL HOSPITAL

VINCENT OBSTETRICS
& GYNECOLOGY

Obstetrical Ultrasound and
Prenatal Diagnostic Center



Prenatal Diagnosis:
Options and Opportunities



Learn about various screening options
including Early Risk Assessment (ERA),
now available to women of all ages. Visit
our website at www.massgeneral.org/obgyn



WHAT IS PRENATAL DIAGNOSIS?

Everybody wants a healthy baby, but 2 to 3 percent of all children are born with a birth defect. Prenatal diagnosis is the identification of birth defects prior to delivery. Since the vast majority of babies are normal, we can give most people reassuring information.

What kinds of birth defects are there?

There are three categories:

- Structural Defects
- Genetic Syndromes
- Chromosomal Disorders

STRUCTURAL DEFECTS

What do you mean by a structural defect?

A structural defect is an abnormality of the formation of a specific organ or body part. Some examples include:

- Hydrocephalus
- Spina bifida
- Several kidney abnormalities
- Clubbed foot
- Cleft lip
- Various types of heart defects

Which babies are most likely to have a structural abnormality?

Most structural abnormalities seem to occur at random in women who have no particular risk factors. However, some women – such as those with poorly controlled diabetes, a family history of a structural abnormality and certain kinds of twins – are at increased risk.

How can I determine if my baby has a structural abnormality?

Structural abnormalities can be detected by ultrasound, typically around 18 weeks. This is often referred to as a second trimester structural survey, since it involves a systematic evaluation of the brain, heart, kidneys, etc.

What about screening with alpha fetoprotein?

Maternal serum alpha fetoprotein (MSAFP) screening has been used to help detect spina bifida and certain other birth defects. Since for the most part these anomalies can be easily detected by a carefully performed second trimester structural survey, we no longer routinely recommend this test.

Are there birth defects that cannot be detected by ultrasound?

Yes, unfortunately, there are. Although many birth defects can be reliably detected by ultrasound, others can only be detected some of the time and some cannot be detected at all.

What can be done if my baby is found to have a birth defect?

The pregnancy is often managed differently. Follow-up ultrasounds are usually obtained. Additional tests may be indicated: if a heart defect is suspected, a pediatric cardiologist performs a fetal echocardiogram, and if a brain abnormality is suspected, we may obtain a fetal MRI. We often offer an amniocentesis. Unfortunately 3D ultrasound is not useful for most birth defects.

An elective delivery may be advised, either by induction of labor or by cesarean section. Some birth defects require surgery or other special treatment soon after delivery, and in these cases the delivery should be in a hospital that can provide those services. In very rare cases, an attempt can be made to try to correct the problem prior to birth.

Plans can be made to help the prospective parents care for the child after birth. It is useful to meet with pediatricians and other specialists who will participate in the care of the child. Some prospective parents want the opportunity to meet with other parents who had similar experiences.

Pregnancy termination is an option.

GENETIC SYNDROMES

What are genetic syndromes?

The blueprint for the human body is 'written' in DNA. The 'words' are called genes. A mistake in the DNA can alter the function of a gene, which can result in a pattern of abnormalities called a genetic syndrome.

How can genetic syndromes be identified?

There are two ways we go about identifying genetic syndromes prenatally. We take a careful family history of both prospective parents. Also, we offer carrier testing based on ethnicity.

FAMILY HISTORY

When taking a family history, we try to identify all individuals in the families of both prospective parents who have a medical condition that could be hereditary and, thus, affect the pregnancy. There are three major patterns of inheritance:

Autosomal recessive disorders occur when both parents, who are apparently healthy, are carriers for the same disorder. Examples are cystic fibrosis and sickle cell disease. There is a 1:4 (25 percent) risk that each of their children will be affected. In this case we can offer a CVS (chorionic villus sampling) or an amniocentesis.

X-linked disorders affect boys more than girls. Examples include muscular dystrophy, hemophilia, and fragile X mental retardation. If the genetic defect is passed from the mother, half of her sons will be affected and half of her daughters will be carriers. Carrier daughters may have mild manifestations of the disease.

Autosomal dominant disorders are passed from parent to child. If either parent has one of these conditions, each of their children (both male and female) has a 50 percent chance of inheriting the same disorder. However, the severity of the disorder in affected individuals is frequently unpredictable.

CARRIER TESTING

Some genetic disorders occur more frequently in certain ethnic groups. Therefore, even in the absence of a family history, we can screen for certain autosomal recessive diseases based on ethnic background. This involves a blood test that determines if both partners carry a faulty copy of the same specific gene, implying a 1:4 (25 percent) risk that each of their children will be affected. In this case, we can offer a CVS or an amniocentesis.

The diseases we commonly screen for are listed in the following table:

Ethnicity	Carrier Testing
European/Caucasian	Cystic fibrosis
Eastern European Jewish	Ashkenazi Jewish Panel
French Canadian	Cystic fibrosis, Tay-Sachs
Mediterranean/Middle Eastern	Cystic fibrosis, hemoglobinopathies
Hispanic	Hemoglobinopathies
African, African-American	Hemoglobinopathies
Caribbean	Hemoglobinopathies
Asian	Hemoglobinopathies

It is likely that in the future additional diseases will be added to this table.

CHROMOSOMAL DISORDERS

What are chromosomal disorders?

The blueprint of the body is “written” in DNA, and genes correspond to words. These words are grouped together into chapters of varying length called chromosomes. We get one set of 23 chromosomes from each parent, for a total of 46. When a baby is conceived with an abnormal number of chromosomes, the most common result is a miscarriage. Sometimes the baby is carried to term and can have varying degrees of problems after birth.

What kinds of chromosomal disorders are there?

Down syndrome is a relatively common chromosome abnormality with which many people are familiar. It results from having three copies of chromosome number 21, so it is also called trisomy 21.

People with Down syndrome almost always have some degree of intellectual or cognitive disability and often have other medical problems. Although these medical problems can be treated, there is no treatment or cure for the underlying chromosomal condition. With a life expectancy of more than 50 years, adults with Down syndrome usually live with family, in group homes, or semi-independently; a minority are able to live completely independently.

How likely is it that my baby has Down syndrome?

The risk of Down syndrome at birth depends on the mother's age:

Mother's Age at Delivery	Probability of Down Syndrome
Younger than 30	Less than 1:1000
34	1:500
37	1:200
40	1:100
43	1:50

Are there other chromosomal disorders besides Down syndrome?

Yes. Some are more severe than Down syndrome: the most important examples are trisomy 13 and trisomy 18. Affected individuals can be profoundly retarded and are often stillborn or die in infancy due to the serious medical problems that are associated with these conditions. Fortunately, these severe chromosomal disorders are much less common at birth than Down syndrome. Also, the structural defects that are associated with these conditions are often recognized at an ultrasound done around 18 weeks.

There are also chromosomal disorders that have manifestations that are milder than Down syndrome, such as sex chromosome disorders. Although affected individuals may have infertility and possibly learning

or behavioral problems, sex chromosome disorders are not associated with mental retardation or major physical handicaps.

Like Down syndrome, the risk for most chromosomal disorders is related to the mother's age.

Can you determine if my baby has a chromosomal disorder?

Yes, but this requires an invasive procedure to obtain a sample of fetal cells from the amniotic fluid or the placenta. By examining the fetal cells, we can determine whether or not the baby has normal chromosomes.

What types of invasive procedures are there?

Amniocentesis (also called amnio) is most often done between 15 and 20 weeks. It takes about 2 weeks to get the results. Amniocentesis involves inserting a needle into the uterus and withdrawing a small amount of the fluid that surrounds the baby. The risk of an amniocentesis causing a miscarriage is so small that it is hard to measure precisely; we think it is about 1:500 or 0.2 percent.

CVS stands for chorionic villus sampling. It involves taking a sample of the placenta either vaginally (using a catheter that is inserted through the cervix) or abdominally (using a needle that is inserted through the abdomen). The position of the placenta determines how the procedure is performed. CVS is done earlier than amnio, typically between 10.5 and 14 weeks, so the results are obtained earlier. However, it is a bit more likely than amnio to cause a miscarriage. We think this happens in 1:100 cases, or 1 percent.

Who should have a CVS or an amnio?

Since there is a risk of miscarriage, only women who are at increased risk of having an affected baby should consider a CVS or amniocentesis. Since age is such an important factor in determining the risk of a chromosomal disorder, women who will be 35 or older at delivery are offered more testing options than are younger women.

If you will be younger than 35 at the time of delivery, please refer to page 11 in this pamphlet.

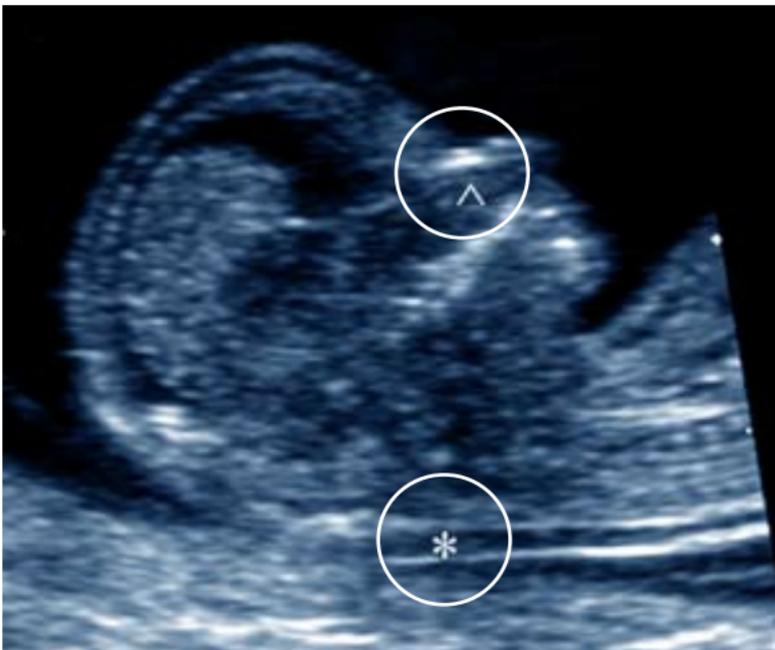
35 OR OLDER AT DELIVERY

Can I go straight to CVS or amniocentesis?

Yes. This option is available for those who desire maximal reassurance that their child has normal chromosomes.

Can't you tell if the baby has Down syndrome from a blood test or by ultrasound?

No. However, we can do ERA – Early Risk Assessment – which is performed between 11.5 and 14 weeks. ERA involves an ultrasound to measure the nuchal translucency (the fluid in the back of the neck of the baby) and to evaluate the nasal bone, which supports the bridge of the nose and tends to be delayed in formation in babies with Down syndrome. In addition, a maternal blood sample is obtained. Based on the combination of the mother's age, the size of the nuchal translucency, the appearance of the nasal bone and the levels of two proteins (PAPP-A and free beta hCG) in maternal blood, the probabilities for Down syndrome, trisomy 13 and trisomy 18 are calculated. For example, the probability of Down syndrome might be 1:1000 or 1:10. Thus, this is not a diagnostic test; rather, it is only an estimate of risk.



A normal fetus. The nuchal translucency () and the nasal bone (^) are marked.*

The nuchal translucency is typically very small, only 1 to 3 mm, and the nasal bone is also very small. It takes special training and expertise to make these assessments accurately. The Fetal Medicine Foundation has played a leading role in standardizing the precise way these assessments should be made and interpreted. They provide certification to those who have additional training, have demonstrated the ability to make these assessments to their satisfaction, and submit their measurements on a regular basis for ongoing analysis and quality review. We feel that only when the nuchal translucency and nasal bone are assessed by someone with certification by the Fetal Medicine Foundation can you be confident that the calculated risks of Down syndrome, trisomy 13 and trisomy 18 are accurate.

An enlarged nuchal translucency or evidence of other problems on ultrasound at the time of ERA will occasionally raise concern for a structural or genetic problem. However, many structural abnormalities will not be detected by ERA, and we urge all women to have a second trimester structural survey at about 18 weeks. Worrisome findings on this ultrasound occasionally cause us to reconsider the option of amniocentesis.

Women who have very low levels of PAPP-A or free beta hCG are at increased risk for fetal growth restriction later in pregnancy. Therefore, they should have additional ultrasounds in the third trimester.

What if I'm too late for ERA?

We can do a second trimester serum screen, often called a quad screen, between 15 and 21.9 weeks. A maternal blood sample is obtained for measurement of four substances: AFP, estriol, hCG and inhibin.

Based on the combination of the mother's age and the quad screen, the probability of Down syndrome is calculated. The quad screen also helps to identify babies at increased risk for certain other abnormalities such as spina bifida.

Like ERA, the quad screen is not a diagnostic test; rather, it is only an estimate of risk. At many centers, including Mass General, this risk can be modified, either up or down, by findings on a second trimester structural survey at about 18 weeks.

The quad screen is almost as accurate as ERA for assessing the risk of Down syndrome. The major advantage of ERA is that the results are available a few weeks earlier.

Can you combine ERA with a quad screen?

Many centers that do first trimester screening without evaluating the nasal bone do exactly this. Compared to ERA, this increases the cost, complexity and most importantly, may delay the results. We feel that evaluation of the nasal bone in the first trimester replaces the quad screen in the second trimester, which then adds very little to the accuracy of the risk estimate.

What are the drawbacks of screening?

Screening is not definitive. Only a CVS or amniocentesis can tell you with certainty if the baby's chromosomes are normal. Even a very low risk of Down syndrome isn't the same as no risk. Both CVS and amniocentesis also detect chromosome disorders other than Down syndrome.

Rarely, a baby will have a large nuchal translucency, but the chromosomes and the rest of the structural survey are normal. In the great majority of cases, these babies are perfectly healthy. However, this baby is at increased risk of being affected by a genetic syndrome of some type, and we can often say nothing further until after the child is born and perhaps not even then. This can be a difficult situation for the prospective parents.

Do I have to choose one of these tests?

No. Many women choose not to have any testing for chromosomal disorders.

What do we need to think about to help us make a decision?

Before you agree to have a test, you should think about what you will do with the information. Many couples would not have a CVS or amniocentesis under any circumstances. They would not undergo pregnancy termination if the baby is affected, and/or they do not accept the risk of miscarriage of a most likely normal baby associated with an invasive procedure. These couples should have neither ERA nor a quad screen. Therefore, although it's difficult, we advise our patients to think about the following questions before they agree to undergo screening:

- *Is this information I want to know prior to delivery?*
- *How do I feel about pregnancy termination?*
- *How do I feel about raising a disadvantaged child?
What impact will this have on my family?
Who will care for an adult with special needs when I am no longer able?*
- *How do I feel about miscarriage?*
- *If I decide not to have testing, will I worry about this until the baby is born?*

Overall, it is important to remember that all of these tests are optional. All decisions regarding prenatal diagnosis are entirely your choice. Discussing the various options with your provider or a genetic counselor is always recommended.



UNDER 35 AT DELIVERY

Can I go straight to CVS or amniocentesis?

In general, we feel that the risks of Down syndrome and other chromosomal abnormalities are too low to warrant the risk and cost of a CVS or amnio. Therefore, doctors are reluctant to do them and insurance companies will generally not reimburse for them.

Can I find out if my baby has Down syndrome?

We can do ERA – Early Risk Assessment – which is performed between 11.5 and 14 weeks. ERA involves an ultrasound to measure the nuchal translucency (the fluid in the back of the neck of the baby) and to evaluate the nasal bone (the nasal bones support the bridge of the nose and tend to be delayed in formation in babies with Down syndrome). In addition, a maternal blood sample is obtained. Based on the combination of the mother's age, the size of the nuchal translucency, the appearance of the nasal bone and the levels of two proteins (PAPP-A and free beta hCG) in maternal blood, the probabilities for Down syndrome, trisomy 13 and trisomy 18 are calculated. For example, the probability of Down syndrome might be 1:1000 or 1:10. Thus, this is not a diagnostic test; rather, it is only an estimate of risk.

If the risk of Down syndrome after ERA is greater than 1:290, if the risk of trisomy 13 or 18 is greater than 1:100, or if there are other worrisome findings on the ultrasound, you will be encouraged to meet with a genetic counselor and will be offered diagnostic testing such as CVS or amniocentesis.

The nuchal translucency is typically very tiny, only 1 to 3 mm, and the nasal bone is also very small. It takes special training and expertise to make these assessments accurately. The Fetal Medicine Foundation has played a leading role in standardizing the precise way these assessments should be made and interpreted. They provide certification to those who have additional training, have demonstrated the ability to

make these assessments to their satisfaction, and submit their data on a regular basis for ongoing analysis and quality review. We feel that only when the nuchal translucency and nasal bone are assessed by someone with certification by the Fetal Medicine Foundation can you be confident that the calculated risks of Down syndrome, trisomy 13 and trisomy 18 are accurate.

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Like ERA, the quad screen is not a diagnostic test; rather it is only an estimate of risk. At many centers, including Mass General, this risk can be modified, either up or down, by findings on a second trimester structural survey at about 18 weeks.

The quad screen is almost as accurate as ERA for assessing the risk of Down syndrome. The major advantage of ERA is that the results are available a few weeks earlier.

Can you combine ERA with second trimester risk assessment?

Many centers that do first trimester screening without evaluating the nasal bone do exactly this. Compared to ERA, this increases the cost, complexity and most importantly, may delay the results. We feel that evaluation of the nasal bone in the first trimester replaces the quad screen in the second trimester, which then adds very little to the accuracy of the risk estimate

What are the drawbacks of screening?

The vast majority of patients who “screen positive” with a risk of Down syndrome greater than 1:290 have normal babies. Consider: 200 women are told they are “screen positive” because they have a risk of Down syndrome of 1:200. Of these 200 women, 199, or 99.5 percent, have unaffected babies. Only one of these 200 babies actually has Down syndrome. That means that 199 women are needlessly alarmed; they may choose either to have a CVS or amnio, subjecting their fetus to a risk of miscarriage, or they will continue to be worried about this until the birth of the child. This is the problem with the false positive rate of screening that you may have heard about.

Furthermore, even if you “screen negative” with a risk of Down syndrome less than 1:290, this is not a guarantee that your child has normal chromosomes. For example, a risk of Down syndrome of 1:500 is not the same as a risk of zero. Also, there are other chromosome disorders besides Down syndrome.

Rarely, a baby will have a large nuchal translucency, but the chromosomes and the rest of the structural survey are normal. In the great majority of cases, these babies are perfectly healthy. However, this baby is at increased risk of being affected by a genetic syndrome of some type, and we can often say nothing further until after the child is born and perhaps not even then. This can be a difficult situation for the prospective parents.

The timing of second trimester serum screening is an issue for some people. The quad screen can

only be done after 15 weeks, and modification of the risk by ultrasound cannot be done until about 18 weeks. Since it takes another two weeks after an amniocentesis to obtain the results, couples who choose amniocentesis after second-trimester risk assessment may not obtain definitive results until 20 weeks.

At this time, not all insurance companies cover ERA. If your insurance company will not cover ERA but you would still like to have it, you do have the option to pay out of pocket. Please check with your provider for up-to-date costs for this test. We bill the insurance companies for the blood work, in lieu of a quad screen.

Do I have to screen my pregnancy for Down syndrome?

No. Some women choose not to have any screening or testing for chromosomal disorders.

What do we need to think about to help us make a decision?

Before you agree to have a test, you should think about what you will do with the information. Many couples would not have a CVS or amniocentesis under any circumstances. They would not undergo pregnancy termination if the baby is affected, and/or they do not accept the risk of miscarriage of a most likely normal baby associated with either CVS or amniocentesis. These couples should have neither ERA nor a quad screen. Therefore, although it's difficult, we advise our patients to think about the following questions:

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Overall, it is important to remember that all of these tests are optional. All decisions regarding prenatal diagnosis are entirely your choice. Discussing the various options with your provider or a genetic counselor is always recommended.



GLOSSARY OF TERMS

Most of the technical terms used are defined throughout this pamphlet. Here are a few others:

Alpha-fetoprotein (AFP): A protein made by the baby. In women carrying a baby with spina bifida and certain other conditions, levels in the mother's blood tend to be a little higher. In women carrying a baby with Down syndrome, levels in the maternal blood tend to be a little lower.

Amniocentesis (amnio): A diagnostic test for chromosome abnormalities that is most often done between 15 and 20 weeks. It involves inserting a needle into the uterus and withdrawing a small amount of the fluid that surrounds the baby.

Ashkenazi Jewish Panel: A group of genetic diseases, such as Tay Sachs disease, that is more common in individuals of Eastern European Jewish ancestry.

Chorionic Villus Sampling (CVS): A diagnostic test for chromosome abnormalities that is performed between 10.5 and 14 weeks. It involves taking a sample of the placenta either vaginally (using a catheter that is inserted through the cervix) or abdominally (using a needle that is inserted through the abdomen).

Genetic syndrome: A medical condition that is caused by changes in an individual's genes (their DNA). It may be passed down through a family or occur for the first time in one individual. Some genetic syndromes are very severe, and others are fairly mild.

Hemoglobinopathies: A group of inherited disorders affecting red blood cells that can result in severe anemia and often other problems. Treatment may involve blood transfusions. Examples are sickle cell disease and thalassemia.

Hydrocephalus: An often serious condition in which fluid builds up in the brain. It is sometimes detected prenatally by ultrasound and may be caused by genetic problems.

Spina bifida: An opening in the spine allowing the spinal cord to be exposed, which often results in varying degrees of physical disability. Surgical repair is needed after birth. The use of a daily multivitamin with folate prior to conception reduces the chance for this condition to develop.

Ultrasound: A technique that uses high frequency sound waves to image the fetal anatomy.





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