ARTICLE

What's on the Genetics Test?

NABT BioClub RECOMMENDATION

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Abstract

The prenatal genetic questionnaire given to every pregnant woman provides a useful basis for teaching genetics concepts.

Key Words: *Prenatal genetic testing; secondary education.*

At some point in a lesson students often ask "Why do I have to know this stuff?" and "What's on the test?" When teaching genetics, the answers can be given preemptively at the beginning of the unit. Ask students for a show of hands: How many intend to one day become parents? The vast majority will respond in the affirmative. Then explain to the students that during pregnancy both mother and father will be asked about genetic testing at two stages. The first stage involves a questionnaire (Figure 1) that the newly pregnant mother and her partner will be asked to fill out at the first prenatal visit. This is the recommended questionnaire from the American College of Obstetrics and Gynecology (ACOG, 2007), which almost all physicians use. After completing the form, the expectant mother will be asked if she wants prenatal genetic testing for certain diseases. Newly pregnant mothers and their partners are often overwhelmed with the amount of information that is required to make informed choices. In order to determine whether she wants to be tested, she will be counseled about the risks of certain diseases, the burdens of certain diseases, and what the options are for testing and treatment.

The second stage is genetic testing of the newborn baby, using blood from a heel stick, on day 1 of life. States vary on the number of diseases screened (National Newborn Screening and Genetics Resource Center, 2011). As an example, Table 1 shows the diseases screened in Connecticut (Connecticut Department of Public Health, 2007).

Students could take these forms home to review with their parents as a resource. Medical information is confidential, so the actual student responses should not be used in class. The newborn testing list can be used to demonstrate the extent of possible genetic testing for treatable diseases but is otherwise best not studied in detail in a survey course. Students could each research one of the 20 questions on the prenatal questionnaire and determine the specifics of each of the diseases and why the question in the table is pertinent. Students in pairs could present a 5-minute role play between a parent-to-be and a genetic counselor, with the parent-to-be formulating expected questions and the counselor providing suitable answers about the disease assigned. With teacher guidance, students will become familiar with many genetics concepts: probability, dominant and recessive traits, sex-linked traits, penetrance, dosage compensation, Barr bodies, pleiotropy, founder effect, aneuploidies, environmental interactions, allele polymorphisms, heterozygote advantage, and the outcomes and ethics of genetic screening. These are all concepts that parents-to-be may need to know to understand genetic risks, but the depth of discussion would obviously be based on the students' grade level. Some of these concepts will be highlighted in the numbered paragraphs that follow (which correspond to the numbered questions on the prenatal questionnaire). The scientific information about each of the diseases was obtained from the Online Mendelian Inheritance in Man (OMIM) website, which is a current and comprehensive database for genetic and chromosomal disorders (http://www.ncbi.nlm.nih.gov/omim/). Notes of interest to students are added.

Newly pregnant mothers and their partners are often overwhelmed with the amount of information that is required to make informed choices.

○ 1. Patient Age 35 Years or Older as of Estimated Date of Delivery

The risk of aneuploidy increases with age, with a faster rate of increase when a woman is in her 30s. In the past, women who were age 35 and pregnant were offered an amniocentesis to determine if the fetus was aneuploid. The maternal age of 35 was chosen because at that age the risk of Down syndrome, the most common autosomal aneuploidy, and the risk of fetal loss from the diagnostic test, an amniocentesis, were both about 1 in 270. That is, at a maternal age of 35, the risk of having a baby born with Down syndrome is the same as the risk of losing a fetus as a result of an amniocentesis. Prior to 2007, only women who were 35 or older were counseled about the risk of Down syndrome and other aneuploidies. Since 2007, however, every woman is offered blood tests and ultrasounds to modify the risk of Down syndrome instead of using the age risk alone. At age 38 the risk of having a baby with Down syndrome is 1 in 175. This risk is higher than

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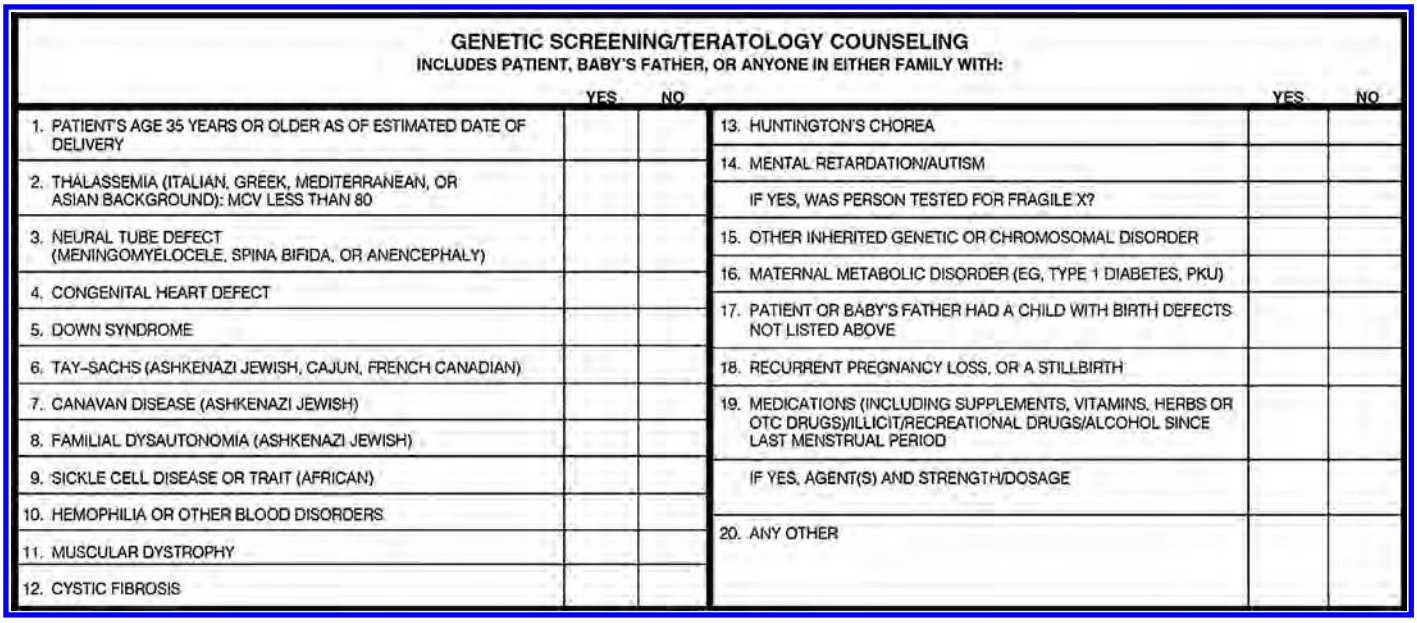

GENETIC SCREENING/TERATOLOGY COUNSELING
INCLUDES PATIENT, BABY'S FATHER, OR ANYONE IN EITHER FAMILY WITH:

	YES	NO		YES	NO
1. PATIENT'S AGE 35 YEARS OR OLDER AS OF ESTIMATED DATE OF DELIVERY			13. HUNTINGTON'S CHOREA		
2. THALASSEMIA (ITALIAN, GREEK, MEDITERRANEAN, OR ASIAN BACKGROUND): MCV LESS THAN 80			14. MENTAL RETARDATION/AUTISM		
			IF YES, WAS PERSON TESTED FOR FRAGILE X?		
3. NEURAL TUBE DEFECT (MENINGOMYELOCELE, SPINA BIFIDA, OR ANENCEPHALY)			15. OTHER INHERITED GENETIC OR CHROMOSOMAL DISORDER		
4. CONGENITAL HEART DEFECT			16. MATERNAL METABOLIC DISORDER (EG, TYPE 1 DIABETES, PKU)		
5. DOWN SYNDROME			17. PATIENT OR BABY'S FATHER HAD A CHILD WITH BIRTH DEFECTS NOT LISTED ABOVE		
6. TAY–SACHS (ASHKENAZI JEWISH, CAJUN, FRENCH CANADIAN)			18. RECURRENT PREGNANCY LOSS, OR A STILLBIRTH		
7. CANAVAN DISEASE (ASHKENAZI JEWISH)			19. MEDICATIONS (INCLUDING SUPPLEMENTS, VITAMINS, HERBS OR OTC DRUGS)/ILLICIT/RECREATIONAL DRUGS/ALCOHOL SINCE LAST MENSTRUAL PERIOD		
8. FAMILIAL DYSAUTONOMIA (ASHKENAZI JEWISH)					
9. SICKLE CELL DISEASE OR TRAIT (AFRICAN)			IF YES, AGENT(S) AND STRENGTH/DOSAGE		
10. HEMOPHILIA OR OTHER BLOOD DISORDERS			20. ANY OTHER		
11. MUSCULAR DYSTROPHY					
12. CYSTIC FIBROSIS					

Figure 1. Genetic screening/teratology counseling (American College of Obstetrics and Gynecology, 2007, used with permission).

the risk of losing a baby because of an amniocentesis, and in the past these women would have been offered an amniocentesis. With a measure of six maternal blood proteins and two ultrasound exams, this risk can be reduced to below 1 in 270 about 94% of the time, with only 9% of women having a risk greater than 1 in 270 after being tested, and therefore offered amniocentesis. So we can pick up 94% of fetuses with Down syndrome by doing an amniocentesis on only 9%, as opposed to using maternal age as the only risk factor, detecting almost 100% by doing an amniocentesis on 100%. The risk is lowered, with fewer amniocenteses needed, but the detection rate drops by 6%. For someone age 25, the *a priori* risk of Down syndrome is 1 in 1200, and the risk can be lowered to less than 1 in 270 about 83% of the time, with only 2% having a risk greater than 1 in 270. The serum protein screening and ultrasounds will detect markers of some autosomal aneuploidies besides Down syndrome but will miss most sex-chromosome aneuploidies. All women receive genetic counseling before the Down syndrome screening tests, and all are offered statistics correlated to their age. An understanding of risk and probability with and without testing is essential to the discussion.

I demonstrate amniocentesis by filling a balloon half with water and half with air. Place a small dot of cooking oil on the upper part of the balloon and insert a 22-gauge needle through the balloon at the site of the dot. Draw off 20 mL of the water in the balloon and then explain that the cells in the fluid are grown in culture, stopped in metaphase, and smeared on a slide after staining. Show several karyotypes of normal and aneuploid cells, including the trisomies 21, 18, and 13, and 47 XXY and 45 XO.

○ 2. Thalassemia

Thalassemia is a genetic anemia characterized by red blood cells that are small, having a low mean corpuscular volume (MCV in the questionnaire), and illustrates the complex genetics of the quaternary structure of a common protein. Either the beta chain or alpha chain of hemoglobin may be affected by mutation, with the gene for the beta chain on chromosome 11 and the two genes for the alpha chain on chromosome 16. The fetus inherits one beta gene from each parent, but two alpha genes from each parent. There is a dosing effect with mutations in both alpha and beta thalassemia, such that lab tests and clinical symptoms reflect the number of mutations in each of the alpha and beta alleles. Thalassemia also is an example of a polymorphism maintained by heterozygote advantage in areas where malaria is endemic. It is a common polymorphism in areas around the Mediterranean Sea, and the name is derived from the Greek words for "sea" (*thalassa*) and "blood" (*haima*).

○ 3. Neural Tube Defect

Neural tube defects are examples of the effects of environment on birth defects. The risk of having a baby with certain defects in the spinal cord and brain can be decreased by taking folic acid supplements prior to and during early pregnancy, when the central nervous system of the fetus is forming. All students should be made aware of this public health recommendation (Centers for Disease Control and Prevention, 2008). In addition, a woman who has had a baby with a neural tube defect in the past should take a tenfold-higher dose of folic acid prior to and during early pregnancy.

○ 4. Congenital Heart Defect

Congenital heart defects have a multifactorial causation. By far, most are not genetic in a Mendelian sense, but if a parent or a sibling of the fetus has a heart defect the fetus may be at increased risk, usually on the order of a 3–5% risk, compared to a background risk of 1%.

○ 5. Down Syndrome

See number 1. Trisomy 21 causes 95% of Down syndrome. The remaining cases are usually due to mosaicism or a translocation of part of the number 21 chromosome to another chromosome. It is important for students to recognize that excess, as well as deficiencies, of chromosomal material can be phenotypically detrimental. Most chromosomal trisomies are incompatible with life. The only three that have been associated with viability after birth are trisomies 21, 18, and 13, and these chromosomes are the autosomes with the least number of genes per chromosome. Most fetal aneuploidies increase in frequency with increasing maternal age. Some, such as 47 XXY or Klinefelter's syndrome, can lead to a relatively normal life. All this information and whether to test for aneuploidies needs to be discussed before the testing is done, because there is no treatment for the fetus and difficult choices may have to be made. For example, almost 60% of mothers who are told they have a fetus affected

Table 1. Newborn screening tests in Connecticut.

Tests
Amino Acid Disorders
• Argininemia or Arginase Deficiency
• Argininosuccinic Aciduria (Argininosuccinase – Deficiency)
• Citrullinemia or Argininosuccinic Acid Synthetase Deficiency
• Homocystinuria or Hypermethionemia
• Hyperprolinemia
• Maple Syrup Urine Disease (MSUD)
• Nonketotic Hyperglycinemia
• Phenylketonuria (PKU)
• Pyroglutamic Acidemia
• Tyrosinemia
Fatty Acid Oxidation Disorders
• Carnitine / Acylcarnitine Translocase Deficiency (CAT)
• Carnitine Palmitoyltransferase Deficiency I (CPT I)
• Carnitine Palmitoyltransferase Deficiency II (CPT II)
• Carnitine Transporter Deficiency
• Ethylmalonic Acidemia (EDA)
• Glutaric Acidemia Type II (GAII) or Multiple acyl-CoA Dehydrogenase Deficiency (MADD)
• LCADD
• LCHADD or Trifunctional Protein Deficiency
• MCADD
• SCADD (Short-Chain ACYL-CoA Dehydrogenase Deficiency)
• VLCADD
• 2,4 Dienoyl CoA Reductase Deficiency
Organic Acid Disorders
• Beta-Ketothiolase Deficiency (BKT) / Mitochondrial Acetoacetyl CoA Thiolase Deficiency
• Glutaric Acidemia Type I (GA-I)
• 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)
• Isovaleric Acidemia (IVA)
• Methylmalonic Acidemia (MMA)
• 3MMC OR 3MCC (3-Methylcrotonyl-CoA Carboxylase Deficiency)
• Multiple CoA Carboxylase Deficiency
• Propionic Acidemia (PPA)
Additional Disorders
• Congenital Adrenal Hyperplasia
• Hemoglobinopathies
• Hypothyroid
• Galactosemia
• Biotinidase Deficiency

by Klinefelter's syndrome will choose abortion, even though this extra X chromosome in a male often causes no symptoms except infertility and is sometimes never diagnosed.

○ 6. Tay-Sachs (Ashkenazi Jewish, Cajun, French Canadian)

Tay-Sachs disease is an autosomal recessive disease caused by a deficiency of the enzyme hexosaminadase A. Symptoms are mental and physical deterioration, with death usually by age 4. It may be an example of a disease with an increased frequency in an ethnic group because of the founder effect. If a harmful gene mutation is present at a higher frequency in a small group, because of segregation of a population or a genetic bottleneck, and this small group tends to intermarry, then this harmful gene mutation may increase in frequency.

○ 7. Canavan Disease (Ashkenazi Jewish)

Canavan disease, like Tay-Sachs, is an autosomal recessive enzyme deficiency with resultant brain dysfunction and death by age 4 if untreated. It may be more prevalent among Ashkenazi Jews because of the factors discussed in number 6. It is not cost effective to offer all genetic tests to all pregnant women. The physician will try to identify women at a higher risk of certain mutations and offer that ethnic group the test. This is what physicians do all the time: identify risk groups and look for disease more intently in those risk groups. No offense is meant to any women when the physician asks about ethnicity.

○ 8. Familial Dysautonomia (Ashkenazi Jewish)

Familial dysautonomia is an autosomal recessive disorder that affects the sensory and autonomic nervous system. Students can have an interesting discussion about what effects the pain insensitivity caused by this disease might have. Another student exercise is to determine the risk to the fetus of this disease as more information is obtained. For example, the overall carrier risk for a parent is 1 in 3000. Therefore, the risk of this disease in a fetus, determined prior to carrier testing, is 1 in 3000 × 1 in 3000 × 1 in 4 (the risk of fetal disease if both parents are carriers), or 1 in 36 million. However, if one parent is of Ashkenazi Jewish ethnicity, the carrier risk in that person is 1 in 30, and the risk to the fetus prior to carrier testing is 1/30 × 1/3000 × 1/4, or 1 in 36,0000. If both parents are Ashkenazi Jewish, the risk to the fetus is 1 in 3600. If one of these parents is tested and found to be a carrier, the risk to the fetus is 1 in 120. If both parents are tested and found to be carriers, the fetal risk is 1 in 4. In this case, ethnicity matters as much as raw probabilities.

○ 9. Sickle Cell Disease or Trait (African)

Sickle cell disease is the classic example of a harmful recessive allele that is a sustained polymorphism due to a survival advantage for heterozygotes, in this case a survival advantage in areas where malaria is endemic. It is also a good example of a single nucleotide substitution causing an amino acid substitution that affects the protein's structure, function, and even electrical charge. This charge difference provides a diagnostic test. Sickle hemoglobin has a substituted neutral valine for the negatively charged glutamic acid in the beta chain of normal hemoglobin A. This single-amino-acid change is enough to cause the separation of the faster-migrating hemoglobin A tetramer from the slower hemoglobin S tetramer when migrating from the cathode on an electrophoresis gel. Carriers will show both bands. The link between nucleotide sequence, amino acid charge and sequence, protein structure, lab test, and clinical effect is explicit with this disease. An ethical debate can revolve around the fact

that sickle cell disease today can often be cured in children (Bernaudin et al., 2007) and possibly adults (Hsieh et al., 2009). The 1-day-old newborn screening includes sickle cell disease. Should society favor prenatal screening for a genetic disease and offer the option of pregnancy termination for a disease with a 95% cure rate?

○ 10. Hemophilia or Other Blood Disorders

Hemophilia is a good example of an X-linked recessive disorder. Two other points can be made. First, human knowledge of genetic effects preceded our knowledge of the gene. The Talmud, a book of Jewish laws dating back a millennium, allows that a male newborn whose two brothers or maternal cousins died of hemorrhage after a circumcision may forgo circumcision. A genetic pedigree done today allows us to find patterns of disease or phenotypes, and these patterns were also detected pre-Mendel. Similarly, Darwin fretted that his children would be less healthy because he had married his first cousin. He knew of the increased risk of disease in children of first-cousin marriages, even though the exact genetic basis was not yet known. Second, mutation is a chance event that has affected not only our evolutionary history but also some political histories. The mutation for hemophilia was passed down from Queen Victoria to her great-grandson Alexei Romanov, the hemophiliac son of the Russian Tsar Nicholas. His disease is thought to have played a role in the events that led to the Russian Revolution in 1917.

○ 11. Muscular Dystrophy

Muscular dystrophy describes a group of heritable muscle disorders. The most common and severe form, Duchenne's muscular dystrophy, is an X-linked recessive disease of the muscles. Because males have only one X chromosome, the disease is manifest in males, but because of random X-inactivation in females there are symptomatic female carriers (Arahata et al., 1989). Barr bodies, dosage compensation, and the fact that females are really mosaics for genes on the X chromosome can be discussed, using calico cats' coat coloration and Duchenne's muscular dystrophy as models.

○ 12. Cystic Fibrosis

Since 2001, obstetricians have been discussing and offering cystic fibrosis (CF) carrier testing to all newly pregnant women. The CF mutation is a good example of the effect of base deletion on the sequence of amino acids in the protein. The most common mutation in the CFTR gene is one that causes a deletion of a phenylalanine at position 508 in the amino acid chain. This is caused by a deletion of three consecutive DNA nucleotides that match up with the phenylalanine in the final translation to protein. The deletion of these nucleotides causes the phenylalanine deletion, but all amino acids after that point are the same as in the normal protein. If there were a one- or two-base deletion or if the three nucleotide deletions were not in a sequence corresponding to one amino acid, most amino acids in the CFTR after position 508 would be different compared with the normal protein. Cystic fibrosis is also an example of pleiotropy, in which a gene affects multiple phenotypic traits. The recurrent lung infections, difficult digestion, and male infertility might seem to be unrelated, but the CFTR mutation affects fluid transport across cell membranes and causes thick extracellular mucus, which is responsible for all the clinical effects.

○ 13. Huntington's Chorea

I introduce Huntington's disease or chorea with a video clip of Woody Guthrie singing the folk song "This Land Is Your Land," for which he wrote the lyrics. He died from Huntington's chorea, an autosomal dominant, late-onset, and lethal disorder of the nervous system. *Chorea* is a descriptive term for the jerky movements made by patients with this disease. There are many diseases that occur late in life, and because natural selection deals with these phenotypes only after reproduction has occurred, the genes for these diseases persist in the population, even if dominant. Huntington's is also a good example of an abnormal gene product causing neurodegeneration even though the cells still have a normal copy of the gene, unlike the loss of function that occurs with recessive disorders (Li & Li, 2004).

○ 14. Mental Retardation & Autism

Both mental retardation and autism are common. There is no proven genetic cause of autism, but both mental retardation and autism-like symptoms may be manifest in certain Mendelian and chromosomal disorders. Fragile X syndrome is a common form of inherited mental retardation. It is a trinucleotide repeat disorder like Huntington's disease and is caused by excessive numbers of CGG repeats in the promoter region for the FMR1 gene on the X chromosome, which causes the X chromosome to appear broken in this region in certain cell cultures. Fragile X should be considered X-linked dominant, given that females with only one mutated X chromosome can be affected, although the disease is milder and less penetrant in females than in males.

○ 15. Other Inherited Genetic or Chromosomal Disorders

There are genetic and chromosomal disorders that are uncommon in a general population but that, if present in a particular family pedigree, will substantially increase the risk to the fetus. For example, the carrier frequency in Caucasians for a nervous system disorder called spinal muscular atrophy is 1 in 35. It is not recommended by ACOG that every pregnant mother be offered carrier testing, but certainly if a pregnant women has a brother with spinal muscular atrophy her risk of being a carrier is not 1 in 35, but 2 out of 3, assuming that she is asymptomatic. Many less common diseases are tested in the 1-day-old newborn, as shown in Table 1, and the purpose is to identify children with genetic disorders that are amenable to early intervention, for example phenylketonuria (PKU).

○ 16. Maternal Metabolic Disorder (e.g., Type 1 Diabetes, PKU)

Newborn testing for PKU was the first newborn genetic screening test. PKU is an interesting disease because the mom's disease may affect the fetus in the womb and because there is a treatment. PKU is an autosomal recessive disorder caused by an abnormal liver enzyme, phenylalanine hydroxylase. Lack of function of this enzyme prevents the conversion of phenylalanine to tyrosine. Symptoms include seizures and mental retardation if untreated. If patients are identified early and treated with a low-phenylalanine diet and other diet modifications, near-normal development can take place. However, if a mother herself has PKU, her lack of adherence to a strict diet may cause excess levels of phenylalanine, which is teratogenic to the fetus, causing fetal microcephaly, mental retardation, and other defects (Committee on Genetics, American Academy of Pediatrics, 2008). Likewise, poorly controlled maternal diabetes can cause metabolic abnormalities in the mother that are teratogenic to the fetus. Women who have either PKU or diabetes should consult a physician before they become pregnant so that their diseases can be put under optimum control before conception in order to decrease the risk of birth defects.

○ 17. Patient or Baby's Father Had a Child with Birth Defects Not Listed

Like congenital heart defects, some birth defects are not strictly Mendelian in inheritance, but their risk can be affected by family history. For example, the risk of cleft palate in the general population is 1 in 1000, but if a woman has had a child with a cleft palate the risk is 30× higher that a subsequent child will be affected.

○ 18. Recurrent Pregnancy Loss, or Stillbirth

Recurrent miscarriage or a stillbirth can be due to a chromosomal rearrangement in the mother or father. These rearrangements may not affect the parent, who has little loss of chromosomal material, but they can cause loss of chromosomal material in meiosis and therefore loss or addition of chromosomal material in the fetus. These chromosomal alterations can cause a miscarriage or affect the normal development of the fetus.

○ 19. Medications (including Supplements, Vitamins, Herbs & Over-the-Counter Drugs) Illicit & Recreational Drugs & Alcohol Since Last Mentrual Period

Anything that goes into a pregnant woman's body may affect the fetus. Prescription drugs for epilepsy, like phenytoin and valproic acid, can cause birth defects. Excessive vitamin A can cause neural tube and other defects in the fetus. It is difficult to test the purity of herbal remedies, and, even if pure, few have been tested and found to be safe in pregnancy, and therefore these are best avoided. It is important for the pregnant woman to know that the background risk of a major birth defect is about 1 in 30. If she has taken any medicine or herbal treatment and her baby ends up with a birth defect, she may feel guilt over having taken the drug even though its use was not related to the birth defect. On the other hand, as mentioned in number 3, supplemental folic acid should be taken prior to and during the first few months of pregnancy in order to decrease the risk of birth defects.

○ 20. Any Others

Many adverse phenotypes and diseases are rare and their causes unknown. If any family history reveals a prevalence of an unusual feature, that trait may have a yet unknown genetic cause or the family may be exposed to environmental teratogens. Patients can be offered consultation with a genetic counselor to receive the most current information.

○ Conclusion

One of the greatest biological drives is to reproduce, and nothing focuses the mind better than planning for the birth of a healthy child. Understanding the genetic and chromosomal risks inherent in reproduction, and making informed decisions about prenatal testing, is a genetic "test" that most students will have to take and one for which we should prepare them.

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