

recommendations

Laboratory Testing During Pregnancy

3rd Edition

Recommendations of the
Prenatal Testing Committee

Wisconsin Association
for Perinatal Care



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The recommendations in this report are intended to serve as a resource and guideline for clinicians who are involved in the design and implementation of prenatal care services. As such, they should not be interpreted as excluding other acceptable courses of care based on medical judgment and patient preferences.

Wisconsin Association for Perinatal Care
McConnell Hall
1010 Mound Street
Madison, WI 53715
608-267-6060
608-267-6089 (facsimile)
E-mail: wapc@perinatalweb.org
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Wisconsin Association for
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WAPC Prenatal Testing Committee

The WAPC Prenatal Testing Committee began its work on 1995, based on the recommendation of prenatal care clinicians throughout the state and staff in the Wisconsin Division of Public Health and the State Laboratory of Hygiene. The Committee was originally charged to study various prenatal laboratory tests and to offer recommendations on what tests should be considered during the course of prenatal care.

The members of the 2005 committee who contributed to the current revisions include:

Committee Chair:

Dwight P. Cruikshank, MD
The Jack A. and Elaine D. Klieger Professor &
Chairman
Department of Obstetrics & Gynecology
Medical College of Wisconsin
Froedtert Memorial Lutheran Hospital
Milwaukee, WI

Ann Rifenberg, CNM, MSN, RN
WI Chapter American College of Nurse Midwives
UW Hospital and Clinics
Madison, WI

Thomas N. Saari, MD, FAAP
WI Chapter, American Academy of Pediatrics
Department of Pediatrics (retired)
Division of Pediatric Infectious Disease
UW School of Medicine
Madison, WI

Committee Members:

Jacqueline Akert, RNC, MSN
Wisconsin Nurse Practitioners in Reproductive Health
Women's OB/GYN Care. S.C.
Waukesha, WI

Dennis Sobczak, MD
WI Section, American College of Obstetricians &
Gynecologists
OB/GYN Affiliates, S.C.
Brookfield, WI

Margo Grady, MS
Genetic Counselor
Meriter Hospital
Madison, WI

Diane Wendland, MD
Family Physician
Cambridge Clinic
Cambridge, WI

Jurgen Herrmann, MD
Great Lakes Genetics
Milwaukee, WI

WAPC Staff:
Ann E. Conway, RN, MSN, MPA
Jennifer Wilen, MPH

Steven Leuthner, MD, MA
Associate Professor of Pediatrics and Bioethics
Medical College of Wisconsin
Milwaukee, WI

Lorraine Meisner, PhD
State Laboratory of Hygiene
Madison, WI



Introduction

Prenatal care has three major components: a comprehensive history, a thorough physical examination, and laboratory testing. The purpose of this report is to address the third component of prenatal care, laboratory testing.

Results from laboratory tests can provide information on chronic conditions such as diabetes, anemia and hypertension; communicable diseases such as sexually transmitted diseases, rubella and hepatitis B; and genetic conditions such as neural tube defects, Down syndrome and other chromosomal abnormalities. With such information, the clinician is better able to determine if a woman may be at risk for pregnancy complications and if further testing or treatment is warranted.

This report offers recommendations on specific laboratory tests that should be considered during the course of prenatal care and describes the circumstances under which the tests should be performed. For example, information on some conditions such as rubella status should be known on all patients. Information on other conditions such as risk for Tay-Sachs disease should be known for those patients at greater risk for that condition. A recommendation on ultrasound scanning is included in the report because it is relevant to prenatal diagnosis. *While the focus of the recommendations is on prenatal testing, many of the conditions could be assessed preconceptionally.*

In developing its recommendations, the Committee relied heavily on positions that have been developed by the major national groups such as the American College of Obstetricians and Gynecologists, American Academy of Pediatrics, the Centers for Disease Control and Prevention, and the United States Public Health Service. The original recommendations were published in April 1997 and revised in October 2000. The current recommendations represent the thinking of Committee members as of the date of publication, January 2006.

Given that the science and technology of laboratory testing is ever changing, the Committee continually reviews the professional literature on prenatal testing. Updated recommendations will be issued as the committee deems it necessary. In an attempt to make these recommendations quickly accessible, clinicians can contact WAPC at 608-267-6060 or look for changes posted on the WAPC Website at:

www.perinatalweb.org

The recommendations in this report are intended to serve as a resource and guideline for clinicians. As such, they should not be interpreted as excluding other acceptable courses of care based upon clinical judgment and patient preferences.



Overview of Committee Recommendations

Patients should receive information from their health care providers about the purpose of all the laboratory tests done during the course of prenatal care.

Information on the following should be known on all prenatal patients, regardless of their risk status.

- Anemia
- Bacteriuria
- Blood Group (ABO) and Rh Testing
- Chlamydia
- Group B Streptococcus (GBS)
- Hepatitis B
- Human Immunodeficiency Virus (HIV)
- Papanicolaou (Pap) Smear
- Red Cell Antibody
- Rubella Immunity
- Syphilis
- Varicella Immunity (Chickenpox)

Information on the following conditions should be known on patients who have been identified to be at risk. Refer to the narrative sections of the specific conditions that are included within this report for information on who is at risk for various conditions. Some conditions, noted by an asterisk, require counseling and acceptance of testing.

- Bacterial Vaginosis
- Cystic Fibrosis*
- Down Syndrome and Trisomy 18*
- Genital Herpes
- Gestational Diabetes
- Gonorrhea
- Hemoglobinopathies
- Neural Tube Defects
- Tay-Sachs and Canavan Disease*
- Tuberculosis

Notes:

- According to state law, the following prenatal conditions discussed in this report are reportable as communicable diseases to your local health officer: chlamydia, genital herpes (first clinical episode only), gonorrhea, hepatitis B, rubella, syphilis, toxoplasmosis, tuberculosis, and varicella. HIV infection is to be reported to the state epidemiologist.
- Clinical references are cited for recommendations that incorporate relatively new approaches to testing. For additional information, the reader could consult a basic obstetrical text such as:

Cunningham, F.G. & Williams, J.W. (2005). *Williams Obstetrics* (22nd ed). New York: McGraw-Hill, Medical Pub. Division.

Gabbe, S.G., Niebyl, J.R., Simpson, J.L. (Eds) (2002) *Obstetrics: Normal and Problem Pregnancies* (4th Ed) New York: Churchill Livingstone.

Anemia, Thalassemia and Hemoglobinopathies

Recommendations

All pregnant women should have a complete blood count with red blood cell indices (CBC with RBC indices). Patients with abnormal values should be evaluated for iron deficiency. Patients with ongoing risk factors should have a repeat hemoglobin/hematocrit at appropriate intervals throughout pregnancy.

Black pregnant women should be screened with a hemoglobin electrophoresis. If this test was previously normal, it need not be repeated. Male partners of patients with an abnormal electrophoresis should also be offered electrophoresis.

Consideration should be given to a hemoglobin electrophoresis in anemic women, especially those of Greek, Corsican or Italian descent, or Latinas of Caribbean origin.

Clinical Considerations and Rationale for Testing

The Centers for Disease Control and Prevention has defined anemia in pregnancy as a hemoglobin concentration less than 11 g/dL (hematocrit 33%) in the first and third trimesters, or 10.5 g/dL (hematocrit 31%) in the second trimester. The reason for the lower cut-off in the second trimester is the so called physiologic anemia of pregnancy, due to the more rapid expansion of maternal plasma volume than red cell mass. Anemia is the most common medical complication of pregnancy, and depending on the population being studied, occurs in 5-25% of pregnant women.

The most common cause of anemia in pregnancy is iron deficiency. The differential diagnosis includes anemia due to blood loss (menorrhagia, intestinal parasites, gastrointestinal bleeding), megaloblastic anemia due to folate deficiency (vitamin B12 deficiency in pregnancy is exceedingly rare), and disorders of hemoglobin synthesis (thalassemia, sickle hemoglobinopathies).

Iron supplementation appears to prevent low hemoglobin at delivery and at six weeks postpartum. Little information is available on pregnancy outcomes for the mother or baby.

Maternal testing of patients in high risk groups for hemoglobinopathies is recommended for several reasons. Maternal hemoglobinopathies may put the pregnancy at risk for such things as preterm birth, stillbirth and growth restriction because of diminished oxygen carrying capacity. Detection of a hemoglobinopathy may have implications for optimum pregnancy management. Detection of the asymptomatic carrier state is important because the fetus may be at risk for a serious hemoglobinopathy if the father is also a carrier of an abnormal hemoglobin. Prenatal diagnosis is available for almost all hemoglobinopathies.

Specific groups at risk for hemoglobinopathies include: Black women (sickle cell disease), women of Italian, Greek or Corsican descent (beta thalassemia and sickle cell disease), and women of Southeastern Asian descent (alpha thalassemia).

Anemia, Thalassemia and Hemoglobinopathies

Testing Procedure

Screening and diagnostic tests commonly used include a CBC with RBC indices and hemoglobin electrophoresis.

A CBC with RBC indices can screen for the carrier state of many hemoglobinopathies. Normal values include an MCV >80, Hb >11 and MCH >27%. Values less than these may indicate iron deficiency or the presence of abnormal hemoglobin. Further testing, including serum iron studies and a hemoglobin electrophoresis, may be indicated.

A Sickledex™ detects 70% of the carriers of sickle cell genes, but does not detect other hemoglobinopathies, such as hemoglobin C or thalassemia, that are relatively prevalent in the same population. It is because of this limitation that the Sickledex™ should not be used to screen for hemoglobinopathies during pregnancy.

A hemoglobin electrophoresis provides qualitative and quantitative analysis of most hemoglobins. Alpha thalassemia will produce a normal hemoglobin electrophoresis and must be detected by DNA analysis.

References

Cuervo, L.G., Mahomed, K. (2001). Treatments for iron deficiency anaemia in pregnancy. *The Cochrane Database of Systematic Reviews Issue 2*. Art. No.: CD003094. DOI: 10.1002/14651858.CD003094.

Cunningham, G., Leveno, K.J., Bloom, S.L., Hauth, J.C., Gilstarp, L.C., & Wenstrom, K.D. (2001). *Williams Obstetrics*, 21st ed. McGraw-Hill: New York.

Bacterial Vaginosis

Recommendation

Women who have risk factors for preterm birth (e.g., previous preterm birth, multiple gestation) should be screened for bacterial vaginosis and treated if positive. There is not sufficient evidence to support routine screening of asymptomatic average risk women.

Clinical Considerations and Rationale for Testing

Bacterial vaginosis is a condition of the vagina in which there is an overgrowth of anaerobic species that produce protease, collagenase and phospholipase A2, and a reduced number of normal vaginal lactobacilli. Pregnant women with bacterial vaginosis may be at increased risk for preterm delivery. Bacterial vaginosis has been found in 15-23% of pregnant women, with up to 50% of patients being asymptomatic. Studies have found an association (two to three times) with preterm labor, premature rupture of membranes and postpartum endometritis. However, there is no convincing evidence that treatment reduces the risk of preterm delivery.

Testing Procedure

Screening is accomplished by clinical examination to determine the presence of a gray discharge at the introitus. The vulva is usually not edematous or erythematous.

The diagnosis can be established when at least three of the following four criteria are met:

- Homogeneous gray discharge that adheres to but is easily wiped from the vaginal vault
- Elevated pH > 4.5
- Fishy odor on addition of 10% KOH to discharge
- Clue cells

Clue cells plus the presence of amine odor has a specificity of 99.5% and a positive predictive value of 98.8%. Elevated pH and presence of odor has a specificity of 96%.

Characteristics of Vaginal Secretions with Bacterial Vaginosis

Characteristic	Women Without Bacterial Vaginosis	Women With Bacterial Vaginosis
pH	Less than or equal to 4.5	Greater than 4.5
Clue Cells	Absent	Present
Lactobacilli: Other bacteria ratio	Greater than 1	Less than 1

Bacterial Vaginosis

References

- American College of Obstetricians and Gynecologists (2001, October). ACOG practice bulletin #198: Bacterial vaginosis screening for prevention of preterm delivery. Washington, D.C.: Author.
- American College of Obstetricians and Gynecologists (2001, October). ACOG practice bulletin #31: Assessment of risk factors for preterm birth: Clinical management guidelines for obstetrician-gynecologists. Washington, D.C.: Author.
- Carey, J.C., Klebanoff, M.A., Hauth, J.C., Hillier, S.L., Thom, E.A., Ernest, J.M., et al. (2000). Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *New England Journal of Medicine*, 342(8),534-40.
- Hiller, S.L., Nugent, R.P., Eschenbach, D.A., Krohn, M.A., Gibbs, R.S., Martin, D.H., et al. (1995). Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. *New England Journal of Medicine*, 333(26),1737- 42.
- United States Preventive Services Task Force (2001). New USPSTF guidelines: Integrating into clinical practice. *American Journal of Preventive Medicine*, 20(3 Sup.), 7-9.
- Vermeulen, G.M. & Bruinse, H.W. (1999). Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: A randomized placebo-controlled double-blind trial. *British Journal of Obstetrics and Gynecology*, 106,652-7.

Bacteriuria

Recommendation

All pregnant women should be screened for asymptomatic bacteriuria early in pregnancy. Those with asymptomatic bacteriuria should be treated. Women with Group B Streptococcus bacteriuria should be given intrapartum antibiotic therapy. A test of cure culture should be done following the antibiotic therapy. Patients at increased risk for recurrent urinary tract infections, particularly patients with hemoglobin SS and AS, should be screened once each trimester. (See section on Group B Streptococcus, page 27.)

Clinical Considerations and Rationale for Testing

Pyelonephritis is the most common, non-obstetric cause of hospitalization during pregnancy. Recurrent pyelonephritis has been implicated as a cause of fetal death and intrauterine growth restriction. While asymptomatic bacteriuria is not increased in pregnancy, it occurs in 2-8% of pregnant women. Pyelonephritis occurs in 1-2% of pregnant women. This increase is caused by bacteria in the presence of stasis and dilation of the upper urinary tract in pregnancy, and undiagnosed or inadequately treated lower urinary tract infection. These infections are usually caused by aerobic gram negative rods. E.coli is responsible for 80-90% of cases of initial infections and 70-80% of recurrent cases. Klebsiella pneumoniae and Proteus species also are important pathogens, particularly in patients who have a history of recurrent infection. Approximately 3-7% of infections will be caused by gram-positive organisms such as group B streptococci, enterococci and staphylococci. Most urinary tract infections can be easily detected by urine culture.

Patients with sickle cell anemia or hemoglobin AS disease are at increased risk for urinary infectious morbidity during pregnancy. Urinary tract infections are common, occurring in 50-67% of women with hemoglobin SS. Patients with acute cystitis usually have symptoms of frequency, dysuria, urgency, suprapubic pain, hesitancy and dribbling. Gross or microscopic hematuria may be present, but fever and systemic symptoms are uncommon.

Two major physiologic changes occur during pregnancy that predispose women to ascending infection of the urinary tract. First, progesterone synthesized by the placenta has an inhibitory effect on ureteral peristalsis and causes ureteral dilatation. Second, the enlarging gravid uterus often compresses the ureters, particularly the right, at the pelvic brim, thus creating additional stasis. Stasis, in turn, facilitates migration of bacteria from the bladder into the ureters and renal parenchyma.

Testing Procedure

Recent data suggests that screening for asymptomatic bacteriuria with a leukocyte esterase-nitrite dipstick is as efficacious as screening by culture and is less costly. However, definitive diagnosis of asymptomatic bacteriuria is based on a clean catch, voided urine culture, revealing greater than 100,000 colonies per ml of a single organism.

References

- Cram, L.F., Zapata, M.I., Toy, E.C., & Baker, B. (2002) Genitourinary infections and their association with preterm labor. *American Family Physician*, 65(2),241-50.
- Rouse, D.J., Andrews, W.W., Goldenberg, R.L., & Owen, J. (1995). Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: A cost-effectiveness and cost-benefit analysis. *Obstetrics & Gynecology*, 86(1),119-23.
- United States Preventive Services Task Force (2005). Screening for asymptomatic bacteriuria: Recommendation statement. *American Family Physician*, 71(8),1575-80.

Blood Group (ABO) and Rh Testing

Recommendation

All pregnant women should have ABO and Rh typing early in *each* pregnancy.

Clinical Considerations and Rationale for Testing

The frequency of the various blood types in Wisconsin is type O: 46%; type A: 42%; type B: 9%; and type AB: 3%. It is important to know a pregnant woman's ABO type so that steps can be taken to assure that type specific blood is available for transfusion if she has an uncommon type. Blood type information is also important if ABO incompatibility is being considered in the differential diagnosis of neonatal jaundice.

In the United States, 15% of white, 8% of black, and 2% of American Indian women are Rh negative. Therefore, depending on race, there is a 75-98% chance that an Rh negative woman's baby has been fathered by an Rh positive man. Because these men can be either heterozygous or homozygous for Rh positivity, overall there is approximately a 70-75% chance that the fetus being carried by an Rh negative woman is Rh positive. In that circumstance, without Rh immunoglobulin (RhoGam) prophylaxis, there is a 16% incidence of maternal isoimmunization in an ABO compatible pregnancy, and a 2% incidence in an ABO incompatible pregnancy.

Greater than 99% of Rh isoimmunization can be prevented with the appropriate use of Rh immunoglobulin administered to the mother. All Rh negative women should receive 300 micrograms of Rh immune globulin if they have a first trimester abortion (spontaneous, induced or ectopic), an amniocentesis or chorionic villus sampling, antepartum bleeding, or significant abdominal trauma during pregnancy. All Rh negative unsensitized women should receive 300 micrograms of Rh immune globulin at 28 weeks gestation. After delivery, the infant of an Rh negative mother should have Rh type determination, and if the infant is found to be Rh positive, additional Rh immune globulin should be administered to the mother within 72 hours of delivery. With such a regimen, more than 99% of cases of Rh isoimmunization can be prevented.

Testing Procedure

ABO and Rh blood typing is a serologic test that uses maternal red cells and reagent sera containing known antibodies. The end point is visible agglutination of the red cells. Most errors in blood typing which have been reported are clerical, with erroneous transcription of the data into the chart, or mixing of samples in the testing laboratory.

Reference

American College of Obstetricians and Gynecologists (1996, August). ACOG educational bulletin #227: Management of isoimmunization in pregnancy. Washington, D.C.: Author.

Chlamydia

Recommendation

Due to the significant incidence of chlamydia infections in all populations, and the potentially serious neonatal sequelae, this committee concurs with the Centers for Disease Control and Prevention and recommends that all pregnant women be screened for chlamydia infection early in pregnancy. Patients with risk factors should be screened again in the third trimester.

Clinical Considerations and Rationale for Testing

Genital infection with *Chlamydia trachomatis* is the most common bacterial sexually transmitted infection in women. Cervical infection with chlamydia is present in 2-25% of women. The lowest reported incidence is 2% in a series of unselected private obstetrical patients. Other series of private obstetrical patients report a 5% incidence, while the incidence approaches 25% in inner-city indigent women attending public clinics.

Women infected with chlamydia may demonstrate mucopurulent cervicitis, urethritis and acute salpingitis. Salpingitis is unusual in pregnancy and probably cannot occur after 12 weeks gestation. Whether maternal chlamydia infection adversely affects pregnancy is controversial. Some studies have shown that recent chlamydia infections increase the incidence of premature rupture of the membranes, preterm labor and chorioamnionitis. Other studies have not supported these findings.

It is clear that there are serious neonatal sequelae for infants born of mothers infected with chlamydia. Chlamydia conjunctivitis occurs in as many as one-third of neonates born to mothers with cervical infection. There is some evidence that neonatal ophthalmic prophylaxis is less effective in preventing chlamydia conjunctivitis than gonorrhoeal. In addition, up to 10% of infants born to mothers with chlamydia cervicitis will develop neonatal chlamydia pneumonia.

The Centers for Disease Control and Prevention recommends that chlamydia diagnostic testing be performed on all pregnant women at the first prenatal visit, and that testing be repeated for high-risk women in the third trimester. The American College of Obstetricians and Gynecologists does not recommend routine testing, but recommends testing in high risk women, defined as those women under age 25, women with a past or present history of other sexually transmitted infections, women with a new sexual partner within the preceding three months, and/or women with multiple sexual partners.

Testing Procedure

Culture methods of detecting chlamydia are time consuming, difficult and expensive. The most useful methods are non-culture methods, such as polymerase chain reaction (PCR), which have shown to be 97% sensitive and 100% specific. Other immunologic and colorimetric tests for the presence of chlamydia antigens are less sensitive and less specific. Non-culture testing for chlamydia is probably best done in laboratories that have experience with the test.

References

American College of Obstetricians and Gynecologists (1994, May). ACOG technical bulletin #190: Gonorrhea and chlamydial infections. Washington, DC.: Author.

Centers for Disease Control and Prevention (2002) Sexually transmitted diseases treatment guidelines. *Morbidity and Mortality Weekly Report* 51 (RR-6),1-78.

Cystic Fibrosis

Recommendations

Screening for the cystic fibrosis (CF) carrier state should be offered to couples in which one or both are Caucasian, and made available to those of other racial/ethnic groups. It should also be offered to individuals with a family history of CF and those whose reproductive partners have CF.

Clinical Considerations and Rationale for Testing

CF is the most common autosomal recessive disease among Caucasians (including Ashkenazi Jews), the incidence of disease being 1/3,300 and the carrier state 1/29. It is much less common among members of other racial/ethnic groups (see Table 1.) Because CF is autosomal recessive, both parents must be carriers to produce an affected child. They need not be carriers of the same mutation. When both partners are carriers, the chance is 1 in 4 that any given offspring will have the disease. Furthermore, two-thirds of their unaffected children will be carriers.

CF is characterized by progressive pulmonary disease. In addition, 85% of affected individuals have pancreatic insufficiency and intestinal malabsorption. Most affected individuals have reduced life expectancy, serious morbidity, and require lifelong medical care.

There are over 900 mutations of the CF gene which cause the disease. The most common in Caucasians (except Ashkenazi Jews) is $\Delta F508$, which accounts for 70% of mutations (30% in Ashkenazi Jews). The most common mutation among Ashkenazi Jews is W1282X. The detection rate with screening for the 25 most common mutations is 80% in non-Jewish Caucasians and 97% in Ashkenazi Jews (see Table 1.) Because of the lower carrier rate and less common mutations in other racial/ethnic groups, their detection rate is considerably lower. Furthermore, since no screening panel can realistically test for all 900 known mutations, a negative test reduces significantly an individual's carrier risk, but not to zero.

Because of the lower carrier risk and disease incidence and the presence of less common mutations in non-white racial/ethnic groups, it is recommended that testing be "made available" to individuals in these groups. The American College of Obstetricians and Gynecologists says that provision of an informational pamphlet is sufficient for such individuals. High risk (white) individuals on the other hand, should be "offered" the test verbally along with appropriate counseling early in prenatal care or preconceptionally.

The usual screening strategy is sequential. The woman is offered screening during preconception counseling or early in prenatal care, and only if she tests positive is screening of her partner carried out. However, in high risk couples where time may be important for early prenatal diagnosis of the fetus, concurrent screening of both parents may be preferred.

If both parents are found to be carriers, prenatal diagnosis may be carried out on fetal DNA obtained either by chorionic villus sampling (CVS) or amniocentesis.

Cystic Fibrosis

Testing Procedure

The standard screening test for CF is a pan-ethnic panel of at least 25 mutations, which includes all CF-causing mutations known to have allele frequency of greater than 0.1% (1 in 1000) among North American patients with CF. Testing for very rare mutations results in only tiny increases in the sensitivity of screening, and is not cost effective. Testing for CF mutations is a highly complex laboratory procedure requiring a facility with sophisticated molecular biology techniques. In addition to testing for the more common mutations, labs must be able “reflex test” carriers they identify for the 4-5 mutations that give false positive results.

Table 1: Approximate Risk

Racial/ethnic Group	Incidence of CF	Carrier Risk	Detection Rate	Carrier Risk After Negative Test
Ashkenazi Jewish	1/3300	1/29	97%	1/930
Other Caucasians	1/3300	1/29	80%	1/140
Latino	1/8500	1/46	57%	1/105
African-American	1/15,300	1/62	69%	1/207
Asian	1/32,000	1/90	low	unknown

Reference

American College of Obstetricians and Gynecologists & American College of Medical Genetics (2001, Oct.)
Preconception and prenatal carrier screening for cystic fibrosis. Washington, D.C.: Author.

Down Syndrome and Trisomy 18

Recommendation

All pregnant women should be counseled about and offered testing for the detection of Down syndrome and Trisomy 18.

Clinical Considerations and Rationale for Testing

The incidence of Down syndrome is about 1/800 births. The incidence of Trisomy 18 is 1/5,000 births. There are several different screening strategies. The incidence of Down syndrome and other chromosome abnormalities increases with advancing maternal age. Therefore, women over 35 may elect to go directly to invasive diagnostic testing, including chorionic villus sampling and amniocentesis.

First Trimester Screening

First trimester screening uses the fetal nuchal translucency measurement by ultrasound and two maternal serum markers, PAPP-A and beta hCG with a detection rate of 82% for Down syndrome and 90% for Trisomy 18 at a false positive rate of 5%. This test is currently limited to facilities that have been certified in the measurement of the nuchal translucency. Nuchal translucency should be done by experienced personnel.

Second Trimester Screening

Maternal serum screening uses three or four markers to identify those women with an increased risk for having a child with Down syndrome, Trisomy 18 or neural tube defect (NTD). Using maternal serum alpha fetoprotein (AFP), human chorionic gonadotrophin (hCG), estriol and inhibin results in a Down syndrome detection rate of about 70% with a false positive rate of 5%. Trisomy 18 is also identified by low levels of AFP, hCG and estriol with a detection rate of 60% and a false positive rate of 0.1%. Neural tube defect detection is approximately 80% for spina bifida and almost 100% for anencephaly.

Maternal serum testing is a screening process and the results should be used by the clinician and the patient to determine if further testing is appropriate and desirable. Screening test results by definition, whether positive or negative, do not necessarily mean that there is or is not an abnormal fetus.

The likelihood of a positive screening result increases with maternal age. Currently, women age 35 years and older should be offered amniocentesis or chorionic villus sampling for the definitive diagnosis of fetal chromosome abnormalities. Women in this age group who decline invasive testing should be counseled about maternal serum screening.

Down Syndrome and Trisomy 18

Testing Procedure

First trimester screening is performed between 11 and 14 weeks gestation. The nuchal translucency is measured by ultrasound and maternal serum levels of PAPP-A and beta hCG are determined. An increased nuchal translucency measurement suggests an increased risk for Down syndrome, Trisomy 18 or heart defects. Low levels of PAPP-A and increased levels of hCG suggest an increased risk for Down syndrome, while low levels of both markers are associated with Trisomy 18.

Second trimester screening is typically performed between 15 and 20 weeks gestation. Maternal serum is obtained for measurement of AFP, hCG and estriol (triple screen), and may include inhibin A (quad screen). In multiple marker screening, maternal age is used in risk interpretation. In general, an increase in Down syndrome risk is associated with low levels of AFP and estriol, and elevated levels of hCG and inhibin. AFP, estriol and hCG are substantially lower than expected in Trisomy 18. This pattern is not affected by gestational age.

Repeat testing based on positive results is not recommended because the low values statistically tend to normalize toward the mean. This will erroneously misclassify some patients' results as negative. An ultrasound is recommended to verify gestational age. If the gestational age is confirmed by ultrasound, then genetic counseling should be offered and amniocentesis considered.

If the multiple marker screen suggests an increased risk for Trisomy 18, confirmation of gestational age is not helpful since this syndrome is often associated with significant fetal growth restriction. Targeted ultrasound for fetal anomalies is helpful, genetic counseling and amniocentesis should be offered for diagnostic confirmation.

Reference

American College of Obstetricians and Gynecologists (2001, May). ACOG practice bulletin #27: Prenatal diagnosis of fetal chromosomal abnormalities. Washington, DC.: Author.

Genital Herpes

Recommendation

Surveillance cultures of pregnant women with a history of Herpes Simplex Virus (HSV) but no visible lesions are not recommended. Cultures or a polymerase chain reaction (PCR) swab from the lesion should be done when a woman has an active lesion to confirm the diagnosis of HSV.

Clinical Considerations and Rationale for Testing

Genital herpes is a sexually transmitted infection causing recurrent vesicles and ulcerations on the genitalia. Approximately 85% of genital herpes is caused by Herpes Simplex Virus Type II (HSV-II) with the remainder caused by HSV-1. This infection can be transmitted vertically at the time of delivery if the mother is actively shedding herpes virus. Neonatal infection can include 1) local skin, eye or oral herpes with or without systemic involvement, 2) CNS infection with significant residua occurring in survivors or, 3) rapidly progressive sepsis-like disease frequently progressing to death. Maternal infection can either be primary localized genital disease of two to three weeks duration or recurrent disease ranging from asymptomatic lesions to those lasting 5 to 10 days. Primary infection presents the greatest risk of transmission to the fetus. Up to 50% of infants delivered vaginally to mothers with primary HSV disease may become infected as compared to a 4% transmission rate to infants born to women with recurrent HSV infection. The true incidence of neonatal HSV infection is unknown because reporting of neonatal herpes to the public health authorities is not mandatory. However, from a study of 58,000 women, it is estimated that the incidence of neonatal herpes is 1/3,200 live births.

There are several mechanisms by which the neonate may acquire HSV infection. These include:

- Vaginal delivery through an infected birth canal
- Ascending infection, especially with ruptured membranes
- Close contact with an infected care giver
- Transplacental transmission (this can only occur with primary infection)

Testing Procedure

Making the diagnosis of HSV in pregnancy, especially at term, is of special importance because of the possibility of adverse neonatal effects. Virus isolation by tissue culture or by PCR swab from suspicious lesions remains the most accurate method of confirming the diagnosis of HSV infection.

It was previously recommended that pregnant women with a history of genital herpes be monitored closely for recurrent infection or asymptomatic viral shedding. This monitoring generally included weekly HSV surveillance cultures of the lower genital tract beginning at 36 weeks gestation. If cultures were negative prior to onset of labor, patients were allowed to deliver vaginally. If cultures were positive, cesarean delivery was recommended. This practice had little effect on the incidence of neonatal HSV infection. Eighty percent of women who deliver infants with HSV infection have no history of infection and no lesions at the time of delivery and would therefore not have met criteria for monitoring in the first place. The current recommendation is that any woman with active lesions or a prodrome at the time of labor or ruptured membranes be delivered by cesarean.

Genital Herpes

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Gestational Diabetes

Recommendation

Universal screening for gestational diabetes mellitus (GDM) is no longer recommended. Rather, selective screening in moderate and high-risk populations should be conducted, based on the recommendations of the American Diabetes Association and the American College of Obstetricians and Gynecologists.

At the first prenatal visit, a health care provider should conduct a risk assessment. Patients are stratified into:

Low Risk:

- Age < 25
- Prepregnancy BMI < 25
- Not a member of a population with a high risk for GDM
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No previous history of adverse obstetric outcomes usually associated with GDM

Moderate Risk:

- Member of a population with a high prevalence of GDM (Latinas, African Americans, American Indians, Southeast Asians and Pacific Islanders)
- Age \geq 25 years
- History of adverse obstetric outcomes usually associated with GDM
- Prepregnancy BMI 26-34
- Known diabetes in a first-degree relative
- History of abnormal glucose tolerance

High Risk: High risk women have the following characteristics in addition to those risks listed for moderate risk women

- Prepregnancy BMI \geq 35
- Strong family history of Type II DM
- Personal history of gestational DM
- Glycosuria
- Prior macrosomic infant

Patients at **high** risk should be screened early in pregnancy and at 24-28 weeks. Patients at **moderate** risk should be screened at 24-28 weeks. Low risk patients need not be screened unless they develop risk factors.

Clinical Considerations and Rationale for Testing

The prevalence of carbohydrate intolerance of pregnancy is 1.5-5% depending upon the population being screened. Considerable controversy exists regarding the clinical significance of gestational diabetes and appropriate screening methodology. Advantages of screening and treating gestational diabetes include preventing fetal macrosomia and its attendant neonatal complications such as hypoglycemia and hyperbilirubinemia, preventing intrauterine death and preventing fetal hyperinsulinemia. Some studies have suggested that fetal hyperinsulinemia

Gestational Diabetes

may have long term consequences such as an increased risk of obesity, hypertension and diabetes in adult life. Disadvantages of screening for gestational diabetes include an increased cesarean rate independent of birthweight. Some studies have failed to demonstrate significant differences in outcomes between patients with treated and untreated gestational diabetes.

Testing Procedure

Screening:

1 hour 50 gram glucose
Abnormal > 140
Fasting not necessary

Diagnosis:

3 hour 100 gram oral glucose tolerance test (GTT)
NPO for at least 8 hours before test
Obtain fasting, one-, two- and three-hour values
Diagnosis is made from 2 abnormal glucose values

Providers usually use one of the two following methods for diagnosis. Normal values are less than the following numbers:

100g Oral Glucose Tolerance Test	O' Sullivan	Fourth International Workshop (Carpenter and Coustan) *
Fasting	105	95
1-hr	190	180
2-hr	165	155
3-hr	145	140

* Referenced in Metzger, B.E. & Coustan, D.R. below

References

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Wisconsin Diabetes Advisory Group (2004). *Wisconsin Essential Diabetes Mellitus Care Guidelines*, http://www.dhfs.state.wi.us/health/diabetes/pdf_files/DMCG/Section12.pdf

Gonorrhea

Recommendation

For women with risk factors, gonorrhea testing should be obtained early in pregnancy and in the third trimester.

Clinical Considerations and Rationale for Testing

The incidence of gonorrhea in pregnancy is considerably less than that of chlamydia. In populations with risk factors, the incidence may be as high as 7%. These risk factors include:

- Young age (less than 25 years)
- Past or present history of other sexually transmitted infections
- History of drug abuse
- Multiple sexual partners, new sexual partner within three months, or partner with multiple sexual partners

Maternal gonorrhea infection may cause cervicitis or urethritis. Salpingitis during pregnancy is uncommon, and probably does not occur after 12 weeks gestation. There is some evidence that there is an increased incidence of preterm labor and preterm rupture of the membranes in women with gonococcal infections.

Gonorrheal infections are a cause of neonatal conjunctivitis. Routine neonatal ophthalmic prophylaxis is quite effective in preventing this condition, however.

Testing Procedure

The gonococcus organism is detected from samples obtained from the endocervical canal by either culture methods or by non-culture methods based on nucleic acid amplification, such as ligase chain reaction (LCR) or polymerase chain reaction (PCR). These molecular methods have been shown to be 98% sensitive and 100% specific.

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Group B Streptococcus (GBS)

Recommendation

All pregnant women should be screened for group B streptococcal (GBS) colonization at 35 to 37 weeks gestation. Results should be communicated in a timely fashion to labor and delivery and pediatric personnel.

Clinical Considerations and Rationale for Testing

Group B streptococcus is found in the intestinal, lower genital and urinary tracts of 20-35% of reproductive age women. Fifty percent of infants born to colonized women become colonized and 2% of colonized infants will develop early-onset sepsis (EOS) with GBS. Prior to the initiation of intrapartum antibiotic prophylaxis (IAP) regimens in the mid 1990's, over 6,000 infants developed EOS annually. Vertical transmission of GBS to the neonate during labor and delivery accounts for 80% of early onset (<7 days of age) GBS disease.

EOS disease may be complicated by meningitis or pneumonitis with the occurrence rate having decreased substantially from 1.70 cases / 1,000 live births in 1992 to 0.32 cases / 1,000 live births in 2003. EOS fatality rates range from 5- 10% with premature infants particularly devastated with case fatalities exceeding 22%. Long-term neurological deficits are seen in 15-30% of GBS survivors when meningitis occurs.

Although a number of maternal and infant risk factors have been associated with neonatal GBS sepsis, a prevention strategy predicated on risk assessment alone will only prevent 68% of EOS. Women with the following risk factors should receive IAP:

- History of GBS bacteriuria
- Previous pregnancy resulting in an infant with EOS
- Intrapartum fever >38°C (100.4° F),
- Premature delivery <37 weeks gestation
- Prolonged rupture of membranes >18 hours

IAP of pregnant women who undergo universal screening for GBS colonization at 35 to 37 weeks gestation results in an 86% reduction of EOS cases, the lowest limits of disease incidence experienced currently. A universal screening strategy does the following:

- Allows more timely initiation of IAP earlier in the course of labor which better ensures a critical 4 hour interval between the onset of antibiotic prophylaxis and delivery of the infant
- Allows identification of GBS antibiotic resistance patterns well in advance of the onset of labor and the subsequent proper choice for IAP
- Provides more time to determine the nature of a history of maternal antibiotic allergy so the correct IAP choice can be made at the onset of labor
- Allows for eliminating the necessity of IAP should a cesarean delivery occur before the onset of labor or the rupture of membranes

Group B Streptococcus (GBS)

Testing Procedure

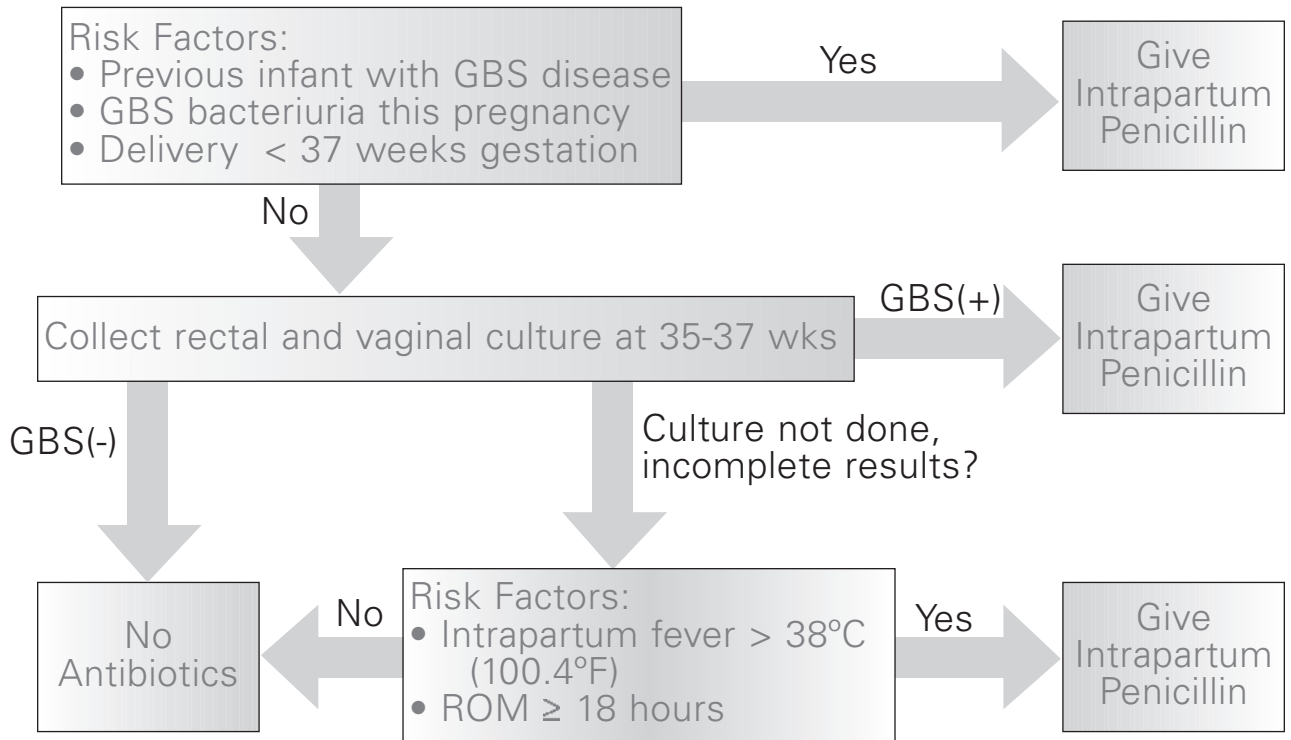
The Centers for Disease Control and Prevention, American College of Obstetricians and Gynecologists and American Academy of Pediatrics recommend that practitioners use screening techniques that incorporate trans-sphincter anorectal and lower vaginal sampling inoculated jointly into a selective enriched growth media to enhance isolation of GBS. Cervical cultures are not reliable and the use of a speculum to obtain a culture is not necessary. Patients with positive GBS cultures at 35 to 37 weeks gestation should always be provided with IAP at the onset of labor. Mothers with unknown or incomplete culture results at the onset of labor but who have a fever $>38^{\circ}\text{C}$ (100.4°F) or ruptured membranes >18 hours should also be given IAP. GBS PCR tests are currently in development, which may allow identification of GBS colonized pregnant women much closer to the onset of labor. Falsely negative cultures at the time of screening occur secondary to sampling of the wrong site (cervix), poor swab storage, inappropriate sample transfer practices and the use of the wrong culture media.

Additional Considerations when Employing the GBS Screening Strategy

- Mothers who present with identifiable risk factors before undergoing GBS screening (GBS bacteriuria, prior delivery of another infant with EOS, GBS disease, preterm delivery < 37 weeks gestation) and mothers with undetermined GBS status who are laboring with risk factors (rupture of membranes > 18 hours, a fever $> 38^{\circ}\text{C}$ (100.4°F), delivery of their infant < 37 weeks gestation) are candidates for IAP.
- Penicillin remains the IAP of choice. The use of broader spectrum ampicillin as an alternative therapy has been associated with an increased incidence of early neonatal fulminant disease due to ampicillin-resistant gram negative bacteria.
- Although most GBS remain sensitive to penicillin, antibiotic resistance to beta-lactam antibiotics has grown in some regions of the country. It would be prudent to periodically test GBS isolates from samples obtained at 35 to 37 weeks gestation for penicillin sensitivity while there is still time to select another more appropriate antibiotic before the onset of labor.
- GBS colonized mothers undergoing cesarean delivery prior to the onset of labor or the rupture of membranes are not candidates for IAP.
- Pregnant women treated for GBS bacteriuria must receive IAP.

Group B Streptococcus (GBS)

2005 Perinatal GBS Prevention Strategy: Screening-Based



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Hepatitis B

Recommendation

All women should be screened for hepatitis B surface antigen as early as possible in the course of each pregnancy.

Rationale for Testing

Twenty-two thousand infants are born each year in the United States to women with chronic hepatitis B disease. Of the 6,000 infants subsequently infected, most are free of symptoms. Nonetheless, up to 90% of infected infants become chronic carriers of the hepatitis B virus (HBV), and 25% of those will eventually succumb to chronic cirrhosis and hepatocellular carcinoma. Selective screening based on maternal risk factors fails to identify more than half of those women who are found infected. Prenatal hepatitis B surface antigen (HBsAg) screening of all pregnant women ensures that every infant at risk is afforded the benefits of hepatitis B immune globulin (HBIG) and HBV vaccine. Immunoprophylaxis of infants is up to 95% effective in preventing the HBV chronic carrier state that is associated with most fatal outcomes. Early identification of HBsAg(+) pregnant women will also permit screening and immunoprophylaxis of household and personal contacts who are put at risk through horizontal transmission or who may themselves harbor unrecognized HBV infection.

HBsAg(-) pregnant women identified as high risk for acquiring hepatitis B (see first paragraph after "Testing Procedure" below) may safely start a full series of hepatitis B vaccine in any trimester. Immunization of high-risk mothers may afford protection to both the 10% of infants who silently acquire hepatitis B in the course of gestation and the 90% of infants who contract the disease from exposure to maternal blood and secretions in the immediate peripartum period.

Perinatal hepatitis B infection is a significant problem in Wisconsin with between 200 and 250 pregnant women documented to have hepatitis B infection in each year. All five Wisconsin public health regions continue to report women found to have hepatitis B surface antigenemia. Although an estimated 86% of all Wisconsin pregnancies are currently screened for hepatitis B, unscreened women who receive limited prenatal care remain the highest risk group for transmitting hepatitis B to their infants. Women who are HIV positive are at an increased risk for hepatitis B.

The American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the American Academy of Family Practice and the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention have supported hepatitis B surface antigen testing of all pregnant women in the United States since 1990.

Hepatitis B

Testing Procedure

HBsAg testing should be performed on a blood sample obtained in the first trimester of pregnancy at the same time other routine prenatal screening tests are done. Women who are initially found to be HBsAg(-) but who are identified as high risk should have additional HBsAg testing done later in the pregnancy if hepatitis B immunization is deferred. Risk factors include:

- Multiple sex partners
- Household and/or sexual contact with the carriers of the hepatitis virus
- Illicit intravenous drug use
- Body piercing or tattooing
- Immigration from highly endemic regions of the world
- Membership in a population with high endemicity (Alaskan Native, Pacific Islander)

Women who arrive at the hospital for delivery without documentation of prenatal hepatitis B screening should have HBsAg testing done on admission or as soon as possible thereafter. Infants of mothers who are found to be HBsAg(+) may still expect full benefit from receiving HBIG and HBV vaccine as effective postpartum prophylaxis for up to one week after delivery.

The long incubation period of HBV (45-160 days; average 120 days), may create a "window" period in which a recently infected woman lacks a positive HBsAg result at the time of testing. Repeat testing later in pregnancy of a HBsAg(-) pregnant woman who fits a high risk profile will reduce the chances of a false negative test, delaying timely immunoprophylaxis of the infant in the immediate postpartum period. Women who are known to be immune and possess hepatitis B surface antibody [HBsAb(+)] through vaccination or prior HBV infection do not require testing.

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Human Immunodeficiency Virus (HIV)

Recommendation

All pregnant women should be counseled about human immunodeficiency virus (HIV) risk factors and disease prevention. Every pregnant woman should be offered and encouraged to undergo HIV testing during pregnancy. Women at increased risk should be offered repeat testing later in pregnancy. Women in labor with unknown serostatus should be offered rapid HIV testing. Early identification of HIV infection leading to aggressive multi-drug antiretroviral therapy markedly reduces the risk of perinatal transmission to the neonate.

Clinical Considerations and Rationale for Testing

Heterosexual women comprise the most rapidly increasing group infected with HIV in the United States. Seven thousand HIV infected women give birth each year in the U.S., resulting in a 13% to 40% vertical transmission rate of the virus from mother to infant. Since 1994, nearly 99% of all new HIV infections in children have occurred by the perinatal route. Between 1996 and 2002, 134 infants were delivered to Wisconsin mothers with HIV, resulting in 11 neonatal infections. Seventy percent of perinatal HIV exposures occurred in southeastern Wisconsin with the remaining cases scattered evenly throughout the rest of the state.

In 1994, the National Institute of Health “AIDS Clinical Trial 076” report demonstrated that the use of zidovudine (AZT) during pregnancy and for the exposed infant during the postpartum period could reduce the perinatal transmission rate to infants from 25% to 8%. Current recommendations now endorse the use of triple antiretroviral therapy for infected mothers as the most effective means to reduce viral loads at the time of delivery. Mothers with undetectable viral loads at parturition reduce the risk of HIV transmission to their infants to less than 1%. Cesarean delivery prior to the onset of labor of mothers with significant viral loads in the third trimester can further reduce transmission risk to the infant. Clinical management issues affected by early maternal HIV identification would allow:

- Assessment of the mother's level of disease activity (CD4+ cell count and viral load).
- Avoidance of increased infant exposure to maternal blood and secretions (scalp electrode and pH testing, early artificial rupture of membranes).
- Timely planning for the route of delivery.
- Advisement against breastfeeding of the infant.
- Early detection of the infant's HIV status to initiate infant treatment protocols.

Counseling and testing strategies restricted to women who report high risk behaviors fail to identify up to 70% of infected women. Risk factors include personal intravenous drug use or sexual partner intravenous drug use, multiple sex partners, partner bisexuality and recipient of blood transfusions or blood products before 1985. Universal counseling and testing provides uniform HIV prevention education as well as testing opportunities for pregnant women in all regions of the state.

The United States Public Health Service, the American College of Obstetricians and Gynecologists and its Wisconsin Chapter, the American Academy of Pediatrics and its Wisconsin Chapter, the Wisconsin Division of Public Health, and the State Medical Society of Wisconsin recommend universal, confidential HIV counseling and HIV testing of all pregnant women. The Wisconsin Association for Perinatal Care Statewide Workgroup on HIV Education and Testing authored a revised and updated HIV prevention position statement in 2003 that provides additional details on implementing office based HIV counseling and testing services.

Human Immunodeficiency Virus (HIV)

HIV Counseling

All pregnant Wisconsin women should be provided with information about HIV risk factors and prevention. Every pregnant woman should be made aware of the benefit of early maternal HIV detection and subsequent treatment to reduce the opportunity for fetal infection and to maximize maternal health. Women not tested during pregnancy should be tested in the peripartum period so that informed decisions regarding breastfeeding and infant management can occur. Wisconsin statutes, as well as those of many other states, require counseling and written informed consent prior to HIV testing. In Wisconsin, this means that, unlike other prenatal tests, specific written informed consent must be obtained prior to conducting HIV testing. The Wisconsin Division of Public Health supports universal counseling and universal voluntary testing of pregnant women for HIV.

HIV Antibody Testing

Women can be tested for the presence of HIV antibody using an enzyme-linked immunosorbent assay (ELISA) at the same time other routine prenatal screening blood tests are done early in pregnancy. A positive ELISA test is repeated on the original sample of blood and, if found positive again, Western blot testing is performed to identify antibodies specific to HIV viral proteins. A positive sequence of ELISA-ELISA-Western blot testing has a false positive rate below 1:100,000. A woman with a negative ELISA test who continues to experience risk factors during her pregnancy should consider repeat testing in the third trimester.

Women who are admitted for labor without documented HIV test results should be strongly encouraged to have a rapid HIV antibody test. There are several FDA approved antibody tests that provide screening results (similar to the ELISA described above), within minutes. A reactive result indicates that the patient may be infected with HIV and must have a Western blot test to confirm infection. Given the turnaround time for a Western blot result, the provider may recommend that the woman begin therapy immediately rather than wait for the Western blot results.

Indeterminate Western blot results can occur as nonspecific cross-reactions in pregnant and parous women, as well as in those with autoimmune diseases who are not HIV infected. Similar indeterminate responses can result from incomplete antibody formation in those who are in the early stages of HIV seroconversion or, alternatively, are in the end-stages of AIDS. Indeterminate results should in no way be considered a positive test, and another blood sample must be immediately sent for repeat testing. Depending on local laboratory processing times, HIV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) testing may be the preferred testing option for follow up of indeterminate Western blot results, particularly in the third trimester.

A positive HIV testing sequence should be discussed directly with the patient as soon as possible.

Recommendations should include:

- Use of AZT during pregnancy for the prevention of perinatal HIV transmission
- Consideration of multi-antiretroviral drug treatment of the pregnant woman to maximize maternal health and minimize HIV viral load (Note: AZT is the only antiretroviral drug approved for the prevention of perinatal spread of HIV and must be included as one of the components of multi-antiretroviral combinations.)
- Discussion about the route of delivery
- Avoidance of breastfeeding

Human Immunodeficiency Virus (HIV)

Hepatitis C testing is not routinely recommended for pregnant women. However, women who have risk factors for Hepatitis C, such as HIV, should be offered testing.

Counseling resources, professional support services and access to community HIV/AIDS programs are available throughout Wisconsin.

References

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Neural Tube Defects

Recommendation

All pregnant women should be counseled about and offered maternal serum alpha-fetoprotein screening for the detection of open neural tube defects. This may be done as part of the triple screen for Down syndrome and trisomy 18.

Clinical Considerations and Rationale for Testing

In the United States, the incidence of neural tube defects (NTDs) is approximately 1 - 2/1,000 births. More than 90% of NTDs occur in pregnancies in which no previous increased risk has been identified. Amniotic fluid and maternal serum alpha-fetoprotein (MS-AFP) levels are elevated in 89-100% of pregnancies complicated by fetal NTDs. Maternal serum screening offers identification of an at-risk woman who can then be offered specific diagnostic testing.

Several developmental abnormalities are associated with an increased concentration of MS-AFP. These include open neural tube defects such as spina bifida or anencephaly. Other developmental defects such as open ventral wall defects are also associated with elevated MS-AFP. In addition to the use of MS-AFP as an aid in diagnosing fetal defects, there is evidence to support that patients who have an elevated level may be at higher risk for complications later in pregnancy. Reported complications include preterm delivery, fetal growth restriction, antepartum hemorrhage and stillbirth.

Maternal serum testing is a screening process, and the results should be used by the clinician and the patient to determine if further testing is appropriate and desirable. Screening test results by definition, whether positive or negative, do not necessarily mean that there is or is not an abnormal fetus.

Testing Procedure

Screening is most accurate when performed between 15 and 20 weeks gestation. Interpretation of the results is dependent upon maternal age, race, weight and gestational age.

Approximately 3% of maternal specimens initially will be considered elevated. The definition of an elevated result varies somewhat among laboratories. A positive result is generally considered to be 2.2 to 2.5 multiples of the median (MoMs) or higher. Exceptions include pregnancies in women with insulin dependent diabetes, which may have a lower MoM cut-off, and multiple gestations which have a higher cut-off. With mildly elevated samples, redrawing the sample may be performed to reduce the risk of a false positive.

When test results are positive, an ultrasound should be performed to confirm gestational age and to identify pregnancies with multiple fetuses, fetal death or fetal structural defects. Using biparietal diameter (BPD) to recalculate the MoM will increase detection rates because fetuses with NTDs have smaller BPDs. Amniocentesis to measure amniotic fluid AFP and acetylcholinesterase (AChE) may help with identification as well, especially in women who are difficult to scan.

Reference

American College of Obstetricians and Gynecologists (2003, July). ACOG practice bulletin #44: Neural tube defects. Washington, D.C.: Author.

Papanicolaou (Pap) Smear

Recommendation

All pregnant women should have a Pap smear early in pregnancy unless there is a documented normal Pap smear in the previous 6 months. A Pap smear should also be taken during the puerperium.

Clinical Considerations and Rationale for Testing

The Pap smear is a screening test for cervical cancer and precancerous lesions (dysplasia). Since the introduction of the test, the mortality rate from invasive cervical cancer has declined by 70%. However, cervical cancer remains a public health problem. Approximately 15,000 cases of invasive cervical cancer occur each year in the United States, and 4,500 women die of the disease. A majority of these deaths occur in women who have not been screened regularly. In addition to screening for cervical cancer and precancerous lesions, the Pap smear detects some cases of human papilloma virus infection, herpes simplex virus infection, and trichomonas and monilial vaginitis. However, it is not considered a screening test for any of these infections.

Testing Procedures and Limitations

While the Pap smear has proven to be one of the most effective tools for cancer screening and cancer prevention, one limitation of its diagnostic accuracy is the reporting of false positives and false negatives. Consequently, these smears should be interpreted in laboratories whose basic quality is known and have licensure through the Center for Medicare and Medical Services, formerly the Health Care Financing Administration, and have been granted a Clinical Laboratory Improvement Act (CLIA) license. Further quality indicators which should be useful in assessing overall quality of interpretation would include the credentials (pathology board-certification and/or cytopathology fellowship and certification) of the pathologist(s) of a given laboratory.

New technologies have become available in the field of gynecologic cytopathology, which include monolayer sample preparation and computerized screening and re-screening. These newer technologies appear to enhance the adequacy and accuracy of Pap smear testing and result in fewer “repeat” Pap smear procedures secondary to inadequate specimens.

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Red Cell Antibody

Recommendation

All pregnant women should be screened for red cell antibodies early in each pregnancy. Additional testing should be performed as clinically warranted.

Clinical Considerations and Rationale for Testing

Maternal sensitization to certain red blood cell antigens present in the fetus puts the fetus at risk for erythroblastosis fetalis and the baby at risk of hemolytic disease of the newborn (HDN). Rh antibody (anti-D) is most commonly responsible for this problem; however, maternal IgG antibodies to several red cell antigens including C, c, E, e, Kell, Duffy, and Kidd may also put the fetus and newborn at risk. The two ways a woman can develop this type of isoimmunization are a previous pregnancy or previous exposure to blood products.

Because of the potential for fetal and neonatal morbidity and mortality in isoimmunized women, it is essential to identify them. Antenatal monitoring with serial antibody titers, ultrasound examinations, and non-stress tests are usually indicated in such individuals. Invasive tests such as amniocentesis and umbilical blood sampling may become necessary, as may therapeutic interventions such as intrauterine fetal transfusion or preterm delivery.

Testing Procedure

The test involves an indirect Coombs' test, also known as an antibody screen. The test is done on maternal serum for the detection of antibodies to red cell antigens. The mother's serum is mixed with pooled red cells containing all of the known red cell antigens. If a mother has antibodies to any of these antigens, her antibodies will coat those cells. Coombs' serum, which is anti-IgG, is then added, and will cause those cells coated with maternal antibody to clump, creating a positive test. If the test is positive, it must be repeated using a "panel" of red cells rather than pooled cells, so that the specific maternal antibody can be identified. It is then necessary to determine the maternal titer of the particular antibody.

Reference

American College of Obstetricians and Gynecologists (1996, August). ACOG educational bulletin #227: Management of isoimmunization in pregnancy. Washington, D.C.: Author.

Rubella Immunity

Recommendation

All women should be tested for rubella immunity preconceptionally or early in their first pregnancy as well as in any subsequent pregnancy if their rubella status is unknown.

Clinical Considerations and Rationale for Testing

Rubella (German measles) is a mild exanthematous disease caused by an RNA virus. This disease has catastrophic effects during pregnancy. The last rubella epidemic in the United States, in 1965, infected 12.5 million people and caused more than 11,000 miscarriages, abortions and stillbirths and 20,000 cases of the congenital rubella syndrome. In 1969, mass immunization of susceptible individuals with live attenuated rubella vaccine was begun. Only nine cases of rubella were reported in the United States in 2004.

Congenital rubella infection may lead to a constellation of abnormalities in the fetus including sensorineural deafness, mental retardation, cardiac malformations, cataracts, retinopathy, microphthalmia, and intrauterine growth restriction. Other findings may include hepatosplenomegaly and thrombocytopenia. The incidence of congenital rubella infection depends on the gestational age at which the mother was infected. Malformations are more common in women infected prior to 12 weeks gestation, whereas other manifestations such as hepatosplenomegaly and thrombocytopenia are more common when infection occurs later in pregnancy.

Immunization of rubella nonimmune women is contraindicated during pregnancy because the live virus crosses the placenta. It should be noted however, that this is a theoretical risk. No congenital anomalies have been reported in the offspring of women inadvertently immunized during pregnancy.

It is important to know the rubella immunity status of a pregnant woman so that she can be alerted to avoid situations where people with rubella may be present, and to immediately report any possible exposure to rubella. It is also useful to know her immune status so that she can be immunized in the immediate puerperium if she is not immune.

Testing Procedure

Serologic testing is the primary method for diagnosing rubella immunity. Several such tests include hemagglutination inhibition, ELISA, immunofluorescence, and radioimmunoassay. All of these tests should be within the capability of any general medical laboratory.

Individuals whose tests are reported as low positive, mid positive, or high positive can be considered immune. Those whose tests are negative are not immune. Those with equivocal tests should be retested.

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Syphilis

Recommendation

All pregnant women should be screened for syphilis early in pregnancy. A second screen should be performed between 28-30 weeks gestation for those women considered to be at high risk for the disease. Repeat serological screening should also be performed at delivery in high risk patients.

Clinical Considerations and Rationale for Testing

Syphilis is a chronic infection by a spirochete that causes lesions that include granuloma formation in many organs. Sexual contact is the usual means of transmission. Any stage of syphilis during pregnancy can result in an infected or affected fetus. Congenital syphilis occurs when maternal spirochetes cross the placenta after the 16th to 18th week of gestation. In rare instances, infection may occur from contact with an infectious lesion during passage through the birth canal. Clinical findings in the infected fetus and baby can range from the totally asymptomatic to severe disease. The disease can be fatal as a consequence of liver failure, pneumonitis, or bleeding diatheses. Evidence of central nervous system disease, as well as involvement of bone, skin, and cartilage may also be present.

One hundred and eleven cases of syphilis were reported in Wisconsin in 2003. However, there was only one reported case of primary or secondary syphilis among women in Wisconsin in the same year and 1,063 cases among women of childbearing age nationwide. In 2000, four cases of congenital syphilis were reported in Wisconsin.

The current Centers for Disease Control and Prevention (CDC) requirements call for reporting of all stillbirths and infants born to women with untreated or inadequately treated syphilis. Penicillin is the treatment of choice. If a woman is allergic to penicillin, proceed with a skin test and desensitization, if necessary. Use of any drug other than penicillin, and treatment <30 days prior to delivery is considered inadequate treatment.

Testing Procedure

Serological tests will almost always be positive by 4 to 6 weeks after contracting the disease. A serological screening test such as the VDRL (Venereal Disease Research Laboratory) or RPR (rapid plasma reagin) should be performed early in pregnancy. A second test should be done between 28-30 weeks gestation for those women considered to be at high risk for the disease. Risk factors include:

- History of drug abuse
- Multiple sexual partners
- New sexual partner within three months
- Partner with multiple sexual partners
- Past or present history of other sexually transmitted infections

Repeat serological screening should be performed at delivery on high risk women. Infant serologic testing should not be conducted on cord blood because the incidence of false positives and false negatives is high. No infant should be discharged from the nursery until the mother's serologic status is known.

Syphilis

References

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Tay-Sachs and Canavan Disease

Recommendation

Screening for the carrier state of Tay-Sachs and Canavan Disease should be offered preconceptionally or in early pregnancy to couples in which one or both are of Ashkenazi Jewish (Eastern European), French Canadian or Cajun descent.

Clinical Considerations and Rationale for Testing

Tay-Sachs disease is an autosomal recessive inborn error of sphingolipid metabolism. Infants born with this disease cannot synthesize biologically active hexosaminidase A (HEXA), the enzyme needed to break down a type of sphingolipid called Gm2 ganglioside. Because infants are unable to break down this substance, it accumulates in body tissues, especially in the brain. This brings on a progressive decline in nervous system function, and death usually occurs by four years of age.

Specifically, Tay-Sachs disease is due to the deficiency of the alpha subunit of hexosaminidase A. Over 50 mutations have been identified in the HEXA gene that affect the subunit and cause Tay-Sachs disease. This disease is found at high frequency in the Ashkenazi Jewish, French Canadian and Cajun populations with carrier frequency of 1/30. Non-Jewish populations and individuals of Sephardic Jewish descent have a carrier frequency of 1/300.

Canavan disease is also an autosomal recessive disorder leading to neurological degeneration and death within the first decade of life. Canavan disease is characterized by a deficiency of the enzyme aspartoacylase, which leads to increased levels of its substrate, N-acetylaspartic acid (NAA). Elevated levels of NAA lead to demyelination and spongy degeneration of the brain. This disease is found predominantly in Ashkenazi Jewish populations. The carrier frequency is 1/40, resulting in clinical disease in 1/6,400 births.

Testing Procedure

Because Tay-Sachs and Canavan Disease are autosomal recessive disorders, both parents need to be carriers to be at risk of having an affected child. The usual screening strategy is sequential. The woman is offered screening during preconception counseling or early in prenatal care, and only if she tests positive is screening of her partner carried out. However, in high-risk couples where time may be important for early prenatal diagnosis of the fetus, concurrent screening of both parents may be preferred.

Carrier detection is based on the amplification of DNA in white blood cells by polymerase chain reaction (PCR) to detect the most common disease-producing mutations. The detection rate is 94% for a Tay-Sachs mutation, 97% for a Canavan mutation in Ashkenazi Jewish populations and 40-50% for non-Jewish carriers of the Canavan mutation.

Other disorders of increased frequency in the Ashkenazi Jewish population that can be tested for include: Bloom syndrome, familial dysautonomia, Fanconi anemia, Gaucher disease, Mucopolysaccharidosis IV, Niemann-Pick disease Type A, torsion dystonia and cystic fibrosis. These are combined and the test is referred to as a "Jewish panel."

Tay-Sachs and Canavan Disease

References

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Toxoplasmosis

Recommendation

Routine screening is not recommended. Pregnant women should:

- Avoid disposing of cat litter.
- Cook meat.
- Wash fruits and vegetables.
- Wear gloves when working in the garden.

Clinical Considerations and Rationale for Testing

Toxoplasmosis is a parasitic infection acquired by ingesting or inhaling oocytes of the protozoan *Toxoplasma gondii*. Oocysts can be found in raw meat or in the feces of domestic cats who hunt rodents. Infection in human adults may be asymptomatic or result in a mild flu-like syndrome. Acute infection occurs in approximately 0.1% of pregnancies.

Congenital infection with toxoplasmosis has been well documented. The incidence of congenital infection varies by gestational age at exposure. Approximately 5% of pregnant women infected in the first trimester will develop intrauterine infection. This rate rises to 30% in the third trimester. The sequelae of congenital toxoplasmosis can be severe, including chorioretinitis, hydrocephaly and microcephaly. Serious sequelae are more common if infection occurs during the first trimester. Three fourths of infected newborns are asymptomatic at birth. It appears that most of these will eventually develop some sequelae of congenital toxoplasmosis infection, which can include chorioretinitis, anemia and convulsions.

If a woman develops toxoplasmosis during pregnancy, therapy with spiramycin should be initiated to decrease the probability of fetal infection. Prenatal diagnosis of fetal toxoplasmosis is possible by amniocentesis. If fetal infection is documented, then additional therapies are added to the regimen. At present, spiramycin is only available in the U.S. specifically for this indication. The pharmaceutical company will provide the drug free of charge if an investigational FDA number is obtained. To obtain the drug, call the Food and Drug Administration (FDA) Division of Special Pathogens at (301)796-1600.

Testing Procedure

Diagnosis of acute or chronic maternal toxoplasmosis infection is made serologically. A rise in IgM on paired specimens drawn three weeks apart is usually required to make the diagnosis. Hemagglutination, immunofluorescence and ELISA antibody determinations are the most common methodologies available. There is great variability in the reliability of toxoplasmosis testing between laboratories. For this reason, the FDA has required confirmation of suspected acute cases at a single reference laboratory.

The low incidence of acute toxoplasmosis during pregnancy, as well as difficulty in diagnosis has led the American College of Obstetricians and Gynecologists to recommend against routine toxoplasmosis testing during pregnancy.

References

American College of Obstetricians and Gynecologists (2000). Practice bulletin #20: Perinatal viral and parasitic infections. Washington, D.C.: Author.

Behrman, R.E. (2004) *Nelson textbook of pediatrics*, 17th ed. W.B. Saunders Company: Philadelphia, PA.

Tuberculosis

Recommendation

Tuberculosis (TB) testing should be performed early in pregnancy on all women in high risk categories.

Clinical Considerations and Rationale for Testing

Tuberculosis is an infection, often life long in duration, caused by one of two species of mycobacterium - *Mycobacterium tuberculosis* and *Mycobacterium bovis*. Reported cases of TB in the United States had declined nearly every year until 1984 when the increase in HIV infections began to reverse this trend. In 2004, there were 95 tuberculosis cases reported in Wisconsin; seven of those cases were also infected with HIV.

The spread of TB infection in the United States is due to two factors: crowded living conditions and individuals who are immunocompromised. Tuberculosis in the United States is concentrated in certain high risk groups that include:

- Those infected with HIV
- Medically underserved populations
- Urban poor
- Alcoholics
- Intravenous drug users
- Homeless people
- Migrant farm workers
- International adoptees
- Employees and residents of correctional and health facilities
- Immigrants from regions with high prevalence of TB

Mode of spread is different for the two species of mycobacteria. Infections of *M. tuberculosis* are caused by the inhalation of infectious particles that are aerosolized by coughing, sneezing, or talking. *M. bovis* results from ingesting unpasteurized milk.

Testing Procedure

Tuberculin testing is best done by intradermal injection of PPD in 0.1cc of solution usually on the volar aspect of the forearm, using a short, beveled needle. Precise injection producing a raised, blanched wheal is necessary. Deeper injection may result in a false-negative result. The reaction is usually read in 48-72 hours, although it can be read accurately up to one week later. A positive test is generally defined as greater than 10 mm of induration, not erythema.

Tuberculosis

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Ultrasound Examination

Recommendation

All pregnant women should be offered a screening obstetric ultrasound between 18 and 20 weeks gestation.

Clinical Considerations and Rationale for Testing

Having accurate information regarding the due date, number of fetuses and presence or absence of major structural fetal anomalies is basic to providing appropriate prenatal care. Standard screening obstetric ultrasound performed at 18 to 20 weeks gestation will provide this information. In addition, identification of placental location as well as uterine, cervical and adnexal anatomy may identify unexpected pathology, which may in turn affect the pregnancy.

Multiple studies have shown screening obstetric ultrasound to significantly reduce post dates pregnancy rates and thus reduce unnecessary testing and inductions of labor. Accurate dating of pregnancies also decreases the rate of tocolysis of erroneously dated preterm labors as well as improves the accuracy of maternal serum screening programs for spina bifida and chromosome abnormalities.

Early diagnosis of multiple gestation provides a wide variety of potential benefits to the infants and parents. Identification of a structurally normal fetus is reassuring to the parents. Detection of fetal anomalies prior to 20 weeks allows time for parental education on the diagnosis and therapeutic options, and gives the physician and other care providers valuable information on care of the affected neonate.

Testing Procedure

Screening ultrasound scanning is best performed at 18 to 20 weeks to maximize the combination of benefits of evaluation of fetal age and identification of fetal anomalies. Individuals performing the scans should follow the established guidelines set by the American College of Obstetricians and Gynecologists and/or the American Institute of Ultrasound in Medicine.

Rates of detection of major fetal anomalies vary considerably. The accuracy of data obtained is directly related to the experience, knowledge and thoroughness of the operator conducting the scan. Some fetal anomalies are not detectable at 18 to 20 weeks gestation because they develop later in the pregnancy. In addition, measurements and visualization of fetal anatomy may vary slightly depending on such factors as the brand of the ultrasound machine, operator skill, position of the fetus and weight of the mother.

References

American College of Obstetricians and Gynecologists (2004, Dec.). ACOG practice bulletin #58: Ultrasonography in pregnancy. Washington, D.C.: Author.

Varicella Immunity (Chickenpox)

Recommendation

A reliable history of varicella disease or immunization is a valid measure of immunity. In the absence of a reliable history, a woman's serologic status should be determined early in pregnancy. If the patient is susceptible to varicella infection, she should be counseled to avoid exposure to infected persons.

Clinical Considerations and Rationale for Testing

Varicella is a highly contagious disease caused by the varicella zoster virus (VZV). VZV has an attack rate of 61-90% among susceptible contacts with an incubation period of 11-21 days (mean, 15 days). More than 90% of cases occur in persons <15 years of age. Approximately 95% of all adults are immune as the result of natural infection. VZV infection conveys lifelong immunity in the immunocompetent host. In addition, approximately 80% of adults who do not recall having infection actually do have immunity. It is anticipated that if current patterns of limited varicella vaccine use in children continue, more young women will enter childbearing age susceptible to varicella than in the past.

While 10% of cases occur in patients >15 years of age or older, 25% of deaths due to varicella are in this age group. The rate, type, scope and severity of complications in adults are substantially higher than in the pediatric population. The most common complications are secondary Group A streptococcal and Staphylococcal aureus bacterial infections of the skin, pneumonia (particularly in women who smoke), dehydration, encephalitis, and hepatitis.

The rate of varicella infection in pregnancy is approximately 1 in 7,000. Systemic maternal VZV infection can cause spontaneous abortion and stillbirth. Ten to 30% of infected pregnant women develop varicella pneumonia, which is associated with maternal mortality rates of 11-40%.

Intrauterine infection can occur regardless of the severity of maternal varicella. Fetal infection can lead to a pattern of birth defects identified as varicella embryopathy, which may include scarring, limb anomalies, growth retardation, microcephaly, cortical atrophy, seizures, developmental delay, chorioretinitis, cataracts, microphthalmia, and gastrointestinal and genitourinary defects. Some severe manifestations of fetal VZV infection may be apparent on ultrasound examination in the second or third trimester. The risk for varicella embryopathy appears to be greatest when maternal infection occurs between 8 and 20 weeks gestation. The risk is estimated to be 1-2%.

Severe varicella of the newborn infant with fatality rates as high as 30% can result when maternal lesions appear between five days before and two days after delivery. Antibody administered to a pregnant woman in the five days before delivery is unlikely to be absorbed and transported across the placenta in sufficient quantities to appreciably protect the infant.

Testing Procedure

Varicella immunity should be determined early in pregnancy by a fluorescent antibody to membrane antigen (FAMA) or an enzyme-linked immunosorbent assay (ELISA). A pregnant patient with no history of VZV infection who is exposed to varicella should have a varicella titer done within 24 to 48 hours.

Varicella Immunity (Chickenpox)

Testing Consequences

If, following a known exposure to varicella, a patient is known to be seronegative to varicella or a varicella titer cannot be obtained in a woman with unknown immune status, varicella-zoster immune globulin (VZIG) should be administered within 96 to 144 hours post exposure. If the woman becomes infected despite prophylaxis, VZIG does not appear to prevent VZV viremia, fetal infection, or varicella embryopathy. Susceptible women may be given varicella vaccine anytime in the postpartum period. Breastfeeding is not a contraindication to receiving varicella vaccine. Pregnant women of negative or unknown varicella immune status should arrange to immunize any varicella susceptible children in the household as soon as practicable. A far greater risk exists to a susceptible mother contracting wild VZV from her infected child than from an exposure to the attenuated varicella vaccine strain used in household contacts.

Acquisition of a vaccine strain of VZV from a vaccinated individual is extremely rare. Infection can only occur through direct contact with vaccine-induced skin lesions that may develop in no more than 5% of people who are vaccinated.

Non-pregnant women of childbearing age who lack immunity or whose immunity cannot be determined should be immunized with two doses of vaccine four to eight weeks apart. Non-pregnant women should be counseled to avoid pregnancy for a period of one month following varicella vaccination. The vaccine should not be given to women who are currently pregnant. Women receiving varicella vaccine during the three month period before pregnancy and inadvertently anytime during pregnancy should be reported to the VARIVAX® Pregnancy Registry at 1-800-986-8999. The duration of immunity from the vaccine is currently not precisely known but, based on the performance of other similar live attenuated viral vaccines, it is most likely life-long.

References

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