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Introduction

This laboratory medicine guideline was developed beginning with preconception issues and proceeding through pregnancy identification, first and second trimester evaluation of fetal health, to delivery and initial evaluation of the newborn. While we have attempted to define the central laboratory medicine issues, this is not a comprehensive listing of all possible events or the medical evaluation that may be required. Our recommendations are based upon the consensus of expert contributors and their experience in their field of expertise. Some issues are not yet fully resolved, and may require us to revisit this topic at some future date. The dietary addition of folic acid has had a significant effect on the incidence of neural tube defects, and we may see some continuation of this trend. The emerging role of first trimester screening for fetal health will continue to develop, and there is some suggestion that it may supplant at least a portion of second trimester screening. The evaluation of the high risk infant at term continues to increase in complexity as does the evaluation of the newborn infant. For this reason we welcome your comments and suggestions. Please send them to John Sherwin at JSHERWIN@dhs.ca.gov.

Chapter 1 Defining Principles in Prenatal Pregnancy Risk Assessment and Reference Values

Gillian Lockitch, MBChB, MD, FRCPC Director, Department of Pathology & Laboratory Medicine, Children's & Women's Health Centre of BC,
Vancouver, BC

Chapter 2 Vaccinations and Serologic Tests During Pregnancy

Philip Rosenthal, MD, FAAP, FACH, FACG, Professor of Pediatrics & Surgery, University of California, San Francisco

Vaccinations During Pregnancy

Vaccination of pregnant women poses theoretical risks to the fetus. Therefore, pregnant women should only receive a vaccine when the vaccine is unlikely to cause harm, the risk for

disease exposure is high, and the infection would pose a significant risk to the mother and/or fetus. When a vaccine is to be given during pregnancy, delay of administration until the second or third trimester, if possible, is a reasonable precaution to minimize concerns of possible teratogenicity. Potential risks to the mother include reactions to the vaccine that could compromise normal gestation and induce premature labor. Such events have not been observed in women immunized during the third trimester of pregnancy. When present, vaccine reactions have been limited to local injection site reactions. (1)

We recommend that women considering pregnancy have a healthcare professional review their immunization status and be given the option to be vaccinated prior to conception.

In the United States, women of childbearing age should be immune to measles, mumps, rubella, tetanus, diphtheria, and poliomyelitis as a result of childhood immunization. The only vaccines routinely recommended for administration to a pregnant woman in the United States are tetanus, diphtheria, and influenza. (1-5) Pregnant women who have not received a diphtheria and tetanus toxoid (dT) booster during the previous 10 years should be given a booster dose. Pregnant women who are unimmunized or partially immunized should complete the primary series. Immunization of the pregnant woman with tetanus toxoid at least 6 weeks before delivery protects the newborn from tetanus neonatornm by stimulating the production of specific IgG antibodies that cross the placenta. Maternal immunization with tetanus toxoid worldwide has dramatically decreased the incidence of neonatal tetanus without evidence of adverse effects on the mother or fetus. (6)

We recommend that pregnant women be immunized with diphtheria and tetanus toxoid (dT) so they are protected prior to delivery.

Women in the second and third trimesters of pregnancy and the early puerperium are at increased risk of complications and hospitalization from influenza. (7) This risk is increased even in the absence of underlying risk factors. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommends trivalent inactivated influenza virus vaccine for all women who will be beyond 14 weeks of pregnancy during the influenza season, and for women with underlying high risk conditions regardless of their stage of pregnancy. (8)

We recommend that pregnant women who will be beyond 14 weeks of pregnancy during the influenza season be vaccinated with the influenza vaccine.

Vaccines Indicated in Special Circumstances During Pregnancy

During epidemic or endemic situations, pregnant women can be immunized with vaccines against poliovirus (inactivated or live attenuated), hepatitis A, yellow fever, and meningococcus. Vaccines that can be administered during pregnancy to women at high risk include the hepatitis B and pneumococcal polysaceharide vaccine.

Routine adult immunization with poliovirus vaccines is not recommended. However, pregnant women at high risk due to endemic or epidemic exposure can receive either oral polio vaccine or inactivated polio vaccine as recommended by the ACIP and the American Academy of Pediatrics. (9,10)

Hepatitis A and hepatitis B vaccines, if indicated, can be administered to a pregnant woman. (1-5) Infants and young children who acquire hepatitis B infection are at increased risk for serious liver disease and even death due to hepatitis, chronic liver disease, and liver cancer compared to adults. Vertical transmission orhepatitis B occurs in infants born to HBsAg-positive mothers with a 90% risk of developing a chronic infection without intervention. Preexposure immunization of susceptible individuals is the most effective means to prevent hepatitis B virus transmission. Risk factors that might indicate hepatitis B immunization of a pregnant woman include injection drug use, multiple sex partners, ajob that exposes one to blood or body fluids, living with someone who is infected, or having sex with someone whom is infected. The currently licensed recombinant DNA HBV vaccines containing HBsAg protein are safe and induce a long-lasting protective antibody response in greater than 90% of adults. Although safety data of these vaccines for the developing fetus are unavailable, no risk would be anticipated because the vaccines contain noninfectious surface antigen.

Vertical transmission of hepatitis A virus from mother to infant is rare. Postexposure immunization with HAV vaccine is recommended in adults. Although pregnant women safety data is limited, the risk to the fetus is considered to be low or nonexistent because the currently licensed vaccines in the United Sates contain inactivated, purified viral proteins obtained from HAV-infected human diploid fibroblast cell cultures.

Pregnancy is in general a contraindication to the administration of all live-virus vaccines. 1-lowever, exceptions should be made when susceptibility and exposure are highly probable and the disease poses a greater risk to the mother and/or fetus than does immunization.

Infection with yellow fever results in a mild to severe viral syndrome associated with high mortality. Immunization with live attenuated virus vaccine (17D strain) is recommended for all 9 months of age or older living or traveling to endemic areas or required by international regulations for travel to and from certain countries. In high-risk areas, women should have been immunized prior to pregnancy. Yellow fever vaccine may be administered to a pregnant woman who is at substantial risk of exposure to infection as might occur with international travel. Yet, it might be prudent to postpone travel until the infant is born, if possible since one possible case of asymptomatic congenital infection was reported in an infant from Trinidad after maternal immunization during the first trimester. (11)

Measles, mumps, rubella, and varicella vaccines that are live-virus vaccines are contraindicated in pregnancy. However, because these diseases can cause significant illness in pregnant women and/or the fetus, every effort should be made to immunize susceptible women against these illnesses before they become pregnant. (1) Women of childbearing age should wait at least 3 months after vaccination with these live-virus vaccines before becoming pregnant. Women, who are pregnant but not vaccinated, should get vaccinated following delivery. Evidence to date suggests that inadvertent administration of rubella vaccine to susceptible pregnant women rarely, if ever, causes congenital defects. The effect of varicella vaccine on the fetus is unknown.
Pregnant women can be immunized with meningococcal vaccine when there is a substantial risk for infection as during epidemics. The vaccine consists of purified bacterial capsular polysaccharides. Pregnant women immunized with a single dose of meningococcal vaccine had good antibody responses, transmitted the antibody through the placenta, and provided protection to the newborn infant during the first few months of life. (12)

S. pneumoniae is the most common cause of invasive bacterial infection and otitis media in children less than *5* years of age. Maternal immunization against pneumococcus is an

alternative strategy to protect young infants until they are able to produce an adequate response to active immunization, especially in high risk groups. Pneumococcal polysaccharide vaccines administered to pregnant women during the third trimester of pregnancy have been safe for pregnant women and their offspring and have transferred modest amounts of antibody to the infant. **(13)**

During pregnancy, certain laboratory tests are performed routinely on all women to monitor the pregnancy. Some tests are done to diagnose problems while others are used as screening tests to determine risks of birth defects or of passing diseases onto the newborn. Tests may be obtained on samples from blood, urine or the cervix. If problems are detected, then many may be treated during the pregnancy. In many states, some of these tests are required on pregnant women by law.

Syphilis. Syphilis is a sexually transmitted disease. All women should be screened serologically for syphilis early in pregnancy with a nontreponemal test (VDRL or RPR) and again at delivery. **(14) In** areas of high prevalence and in patients at high risk for syphilis, an additional nontreponemal serum test should be performed at the beginning of the third trimester of pregnancy (week 28). During pregnancy, low-titer false positive nontreponemal antibody tests may

occur. The nontreponemal antibody test should be confirmed as false positive with a treponemal antibody test (FTA-ABS). When a pregnant woman has a reactive nontreponemal test result and a persistently negative treponemal test result, a false positive test is confirmed.

We recommend that all pregnant women be screened for syphilis early in pregnancy.

Rubella. Postpubertal women without documentation of presumptive evidence of rubella immunity should be immunized, unless they are pregnant. (15) Postpubertal females should be advised not to become pregnant for 3 months following rubella vaccination. Routine prenatal screening for rubella immunity should be undertaken, and rubella vaccine administered to susceptible women during the immediate postpartum period before discharge.

We recommend routine prenatal screening for rubella immunity, and rubella vaccine administration to susceptible women 3 months prior to conception or immediately postpartum.

Hepatitis B virus. Serologic testing of all pregnant women for the hepatitis B surface antigen (HBsAg) is essential for identifying infants who require postexposure immunoprophylaxis beginning at birth to prevent perinatal hepatitis B viral infection. (16) In high-risk individuals, repeat testing may be indicated in the third trimester. Postexposure immunoprophylaxis with hepatitis B immune globulin (HBIG) and the hepatitis B vaccine can substantially reduce the incidence of maternal-neonatal transmission of hepatitis B virus.

We recommend serologic testing of all pregnant women for hepatitis B by the hepatitis B surface antigen test.

Hepatitis C virus. Seroprevalence among pregnant women in the United States is estimated at 1 -2%. Maternal-neonatal transmission is estimated at *5%.* Maternal coinfection with human immunodeficiency virus (HIV) has been associated with an increased risk of perinatal transmission of HCV (6-fold increase). Hepatitis C can lead to cirrhosis, hepatocellular carcinoma, hepatic failure and death. Hepatitis C currently is the leading indication for liver transplantation in the United States. Both the American Academy of Pediatrics and the Centers for Disease Control and prevention recommend that all children born to women who are infected with hepatitis C virus or have risk factors for infection be screened for hepatitis C. (17) Most infected women are asymptomatic and unaware of their infection. The 2 major tests for the laboratory diagnosis of IICV infection are antibody assays for anti-HCV and assays to detect HCV nucleic acid (RNA). Diagnosis by antibody assays involves an initial screening enzyme immunoassay (ELA). Repeated positive results are confirmed by a recombinant immunoblot assay (RIBA). Both assays detect IgG antibodies-no 1gM assays are available. PC'R assays are used commonly in clinical practice in the early diagnosis of infection and to identify infection in infants when maternal serum antibody (IgG) which crosses the placenta interferes with the ability to detect antibody produced by the infant. Universal testing of all pregnant women for hepatitis C may not be cost effective currently. However, selective testing based on risk factors is definitely warranted.

We recommend serologic testing of pregnant women for hepatitis C if clinically indicated or requested by a screening enzyme immunoassay (EIA).

Human Immunodeficiency virus (HIV). HIV is the virus that causes acquired immunodeficiency syndrome (AIDS). More than 90% of infected children in the United Sates

acquired their HIV infection from their mothers. A substantial decrease in recent years in perinatal AIDS is due to the successful intervention with zidovudine administered to HI V-infected pregnant women. It is recommended that all pregnant women be offered counseling and testing with consent for HIV. **(18)** Testing for HIV infection is unlike most routine blood testing because of risks for discrimination in jobs, school, and child care. Adults develop serum antibody to HIV by 6-12 weeks after infection. Infants born to HI

V-infected mothers have transpiacentally acquired antibody and thus test seropositive from the time of birth. HIV nucleic acid detection by PCR of DNA extracted from peripheral blood mononuclear cells is the preferred test for diagnosis of HIV infection in infants. Infants born to HI V-infected mothers should be tested by HIV DNA PCR during the first 48 hours of life. Because of the possibility of maternal blood contamination, umbilical cord blood should not be used for testing. A second test should be performed at 1-2 months of age. A third test is recommended at 3-6 months of age. Any time a test is positive, a repeat test should be immediately obtained for confirmation. An infant is considered infected if 2 separate samples are positive. Infection can be excluded if 2 HIV DNA PCR samples are negative performed beyond I month of age and or I sample was obtained at 4 months of age or older.

We recommend that all pregnant women have their HIV status evaluated by an appropriate antibody test after informed consent. Counseling must be provided regarding the results of testing.

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Chapter 3 Preconception Care Issues and Pregnancy Diagnosis

Sylvie Langlois, M.D., FRCPC, FCFMG, Clinical and Molecular Geneticist, Director, Medical Genetics, Children's and Women's Health Centre of BC, Vancouver, BC

Chapter 4 First Trimester Prenatal Screening and Diagnostic Evaluation

First trimester prenatal screening and diagnostic evaluation.

Dr Stephanie Rhone[1], MD, RDMS, FRCSC and Peter von Dadelszen[2,3], MBChB, DPhil, FRCSC;
Clinical Assistant Professor[1] and Assistant Professor[2], Department of Obstetrics and Gynaecology and Centre for Healthcare Innovation and Improvement[3], University of British Columbia and the Children's and Women's Health Centre of British Columbia, Vancouver, BC, Canada.

Outline.

This document will cover the utility of the 11-14 week scan, details of the nuchal translucency (NT) technique, the association between NT and chromosomal defects, combined screening methods for chromosomal defects, and the significance of an abnormal NT in the presence of a normal karyotype. Also covered is the integrated clinical, ultrasound, and laboratory management of ectopic pregnancy.