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СПЕЦИФИЧЕСКИЕ ИНФЕКЦИИ У БЕРЕМЕННЫХ

Учебно-методическое пособие
для студентов 4–6 курсов факультета по подготовке специалистов
для зарубежных стран медицинских вузов

MATERNAL INFECTIONS DURING PREGNANCY

Teaching workbook
for 4–6th year students of the Faculty on preparation of experts
for foreign countries of medical highest educational institutions

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ABBREVIATIONS

Abbr.	Meaning
CLD	Chronic liver disease
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CSF	Cerebrospinal fluid
DFA	Direct fluorescent antibody
DGI	Disseminated gonococcal infection
dL	Deciliter
DNA	Deoxyribonucleic acid
EC	Emergency contraception
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EPT	Expedited partner therapy
FDA	Food and Drug Administration
FTA-ABS	Fluorescent treponemal antibody absorbed
gG	Glycoprotein G
GNID	Gram-negative intracellular diplococci
HAART	Highly active antiretroviral therapy
HAV	Hepatitis A virus
HBIG	Hepatitis B immune globulin
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFA	Immunofluorescence assay
IUD	Intrauterine device
MAC	Mycobacterium avium complex
MIC	Minimum inhibitory concentration
MSM	Men who have sex with men
N-9	Nonoxynol-9
NAAT	Nucleic acid amplification test
NGU	Nongonococcal urethritis
nPEP	Nonoccupational postexposure prophylaxis
Pap	Papanicolaou
PCR	Polymerase chain reaction

PEP	Postexposure prophylaxis
PID	Pelvic inflammatory disease
PPV	Positive predictive value
PROM	Premature rupture of membranes
QRNG	Quinolone-resistant N eisseria gonorrhoeae
R.D.S	Respiratory distress syndrome
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT-PCR	Reverse transcriptase polymerase chain reaction
RVVC	Recurrent vulvovaginal candidiasis
SIL	Squamous intraepithelial lesion
STD	Sexually transmitted disease
TCA	Trichloroacetic acid
TE	Toxoplasmic encephalitis
TP-PA	Treponema pallidum particle agglutation
UTI	Urinary tract infection
VDRL	Venereal Disease Research Laboratory
VVC	Vulvovaginal candidiasis
WB	Western blot
WBC	White blood count
WSW	Women who have sex with women

PREFACE

Infectious diseases remain a leading cause of maternal and neonatal mortality during pregnancy, labor, and the puerperium. Epidemiologic statistics have provided evidence for their role in preterm labor, preterm premature rupture of the membranes, intrauterine growth restriction, neonatal conjunctivitis, neonatal pneumonia, and congenital syphilis. Although profound changes are observed in the immune system during pregnancy, it remains unclear whether pregnant women are more susceptible to infection. Pregnancy complicates the management of infectious diseases due to concerns regarding fetal well-being and the effect of pregnancy on antimicrobial agents. The obstetrician should be well versed in the identification and management of pregnancy complicated with maternal infections.

1. PREGNANCY AND INFECTIONS

The most common pregnancy and puerperium infections result from ascending contamination of the uterine cavity from the lower genital tract flora and include such conditions as intraamniotic infection (also referred to as chorioamnionitis), urinary tract infection and pyelonephritis, postpartum endometritis, and (rarely) pelvic inflammatory disease. Such infections are often polymicrobial in nature, involving both aerobic and anaerobic organisms. Offending organisms may include the following:

1. Pyogenic (50 %):

- Anaerobes: Peptostreptococcus spp., Prevotella spp., Bac-teroides fragilis group, Fusibacterium spp., Porphyromonas asacchrolyticus, Clostridium spp., Mobiluncus spp.
- Aerobes: Groups A, B, and D streptococci, enterococci, Escherichia coli, Klebsiella spp., Proteus spp., Staphylococcus aureus, Gardnerella vaginalis.

2. Sexually transmitted disease (STD):

N. gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Herpes simplex virus type II, Human papilloma virus, Gardnerella vaginalis (Haemophilus vaginalis), Haemophilus ducreyi, Donovan bodies, HIV I or II, etc.

3. Parasitic: Trichomonas vaginalis.

4. Fungal: Candida albicans.

5. Viral: Herpes simplex virus type II, Human papilloma virus, HIV, Condylomata accuminata.

6. Tubercular: Mycobacterium tuberculosis.

The altered immune state of pregnancy increases the risk of other infections for the adult host. Both the frequency and the severity of infection can be increased. There are conflicting laboratory data about a reduced immunologic response during pregnancy. Evaluation of immunity is divided into two categories: humoral and cellular. Most of the studies of humoral immune response in pregnancy show reactions similar to those found in nonpregnant women. In contrast, the cellular immune response has generally been diminished. For example, Finland and Dublin's detailed study, published in 1939, of a large number of Boston women who had a pneumococcal pneumonia doc- umented a death rate that was higher in pregnant than in non-pregnant women, particularly when the disease was contracted in the third trimester. The increased severity of infection in pregnant women is not limited to bacterial infections. Viruses are also a problem. In the influenza pandemic of 1957, death was much more common among pregnant women. Protozoal disease and systemic fungal disease can also be serious. For example, pregnant women have an increase in both the incidence and the complications of malaria and, in endemic regions, coccidioidomycosis is a leading cause of maternal death. All these different disease entities, caused by

bacteria, viruses, protozoa, and fungi, share two similar traits: they are normally held in check by cell-mediated immune mechanisms, and all are more serious in pregnancy.

For infectious disease control, the strategies fit into three major groupings: treatment, immunization, and prevention strategies. The traditional approach is the treatment of an established infection and prevention before pregnancy (preconception) and those women during pregnancy. Obstetricians must take a more active role in the immunization of adult women. When young women become sexually active, they switch their primary care from the pediatrician to the obstetrician-gynecologist. In the future, we will need to become more attuned to preventive medicine strategies in women. The preconception period is a window of opportunity for the prevention of infections in women.

Metabolism and elimination of drugs are also altered in pregnancy, with hormonally mediated reductions in hepatic metabolism and increases in renal clearance. The net effect of pregnancy-induced alterations on drug pharmacokinetics and efficacy is often unpredictable. Changes in drug absorption, via reductions in gastric emptying and acid secretion, increased intestinal motility, and increased pulmonary tidal volume (which may affect inhaled drugs), are observed. Furthermore, the volume of distribution for drugs is significantly enlarged during pregnancy with increases in plasma volume of 50 %, total body water of 7 to 8 L, and body fat of 20 to 40 %. Although these volume alterations would be expected to decrease drug levels, albumin concentrations decline, and free fatty acid and lipoprotein values rise, leading to increases in circulating free (biologically active) drug levels.

1.1. RECOMMENDED SCREENING TESTS BY PERINATALY TRANSMITTED INFECTIONS

Intrauterine or perinatally transmitted STDs can have severely debilitating effects on pregnant women, their partners, and their fetuses. All pregnant women and their sex partners should be asked about STDs, counseled about the possibility of perinatal infections, and provided access to screening and treatment, if needed. Recommendations to screen pregnant women for STDs are based on disease severity and sequelae, prevalence in the population, costs, medico-legal considerations (e.g., state laws), and other factors. The screening recommendations in this report are generally broader (i.e., more pregnant women will be screened for more STDs than would by following other screening recommendations) and are consistent with other CDC guidelines.

1. All pregnant women in the United States should be screened for HIV infection at the first prenatal visit, even if they have been previously tested. Screening should be conducted after the woman is notified of the need to be screened for HIV as part of the routine panel of prenatal tests. For women who decline HIV

testing, providers should address their objections, and when appropriate, continue to encourage testing. Women who decline testing because they have had a previous negative HIV test should be informed of the importance of retesting during each pregnancy. Testing pregnant women and treating those who are infected are vital not only to maintain the health of the woman, but to reduce perinatal transmission of HIV through available antiretroviral and obstetrical interventions. Retesting in the third trimester (preferably before 36 weeks' gestation) is recommended for women Recommendations and Reports at high risk for acquiring HIV infection (e.g., women who use illicit drugs, have STDs during pregnancy, have multiple sex partners during pregnancy, live in areas with high HIV prevalence, or have partners with HIV infection). Rapid HIV screening should be performed on any woman in labor who has not been screened for HIV during pregnancy unless she declines. If a rapid HIV test result is positive in these women, antiretroviral prophylaxis should be administered without waiting for the results of the confirmatory test.

2. A serologic test for syphilis should be performed for all pregnant women at the first prenatal visit. When access to prenatal care is not optimal, rapid plasma reagin (RPR) card test screening (and treatment, if that test is reactive) should be performed at the time that a pregnancy is confirmed. Women who are at high risk for syphilis or live in areas of high syphilis morbidity should be screened again early in the third trimester (at approximately 28 weeks' gestation) and at delivery. Some states require all women to be screened at delivery. Neonates should not be discharged from the hospital unless the syphilis serologic status of the mother has been determined at least one time during pregnancy and preferably again at delivery if at risk. Any woman who delivers a stillborn infant should be tested for syphilis.

3. All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg) at the first prenatal visit even if they have been previously vaccinated or tested. Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., having had more than one sex partner in the previous 6 months, evaluation or treatment for an STD, recent or current injection-drug use, and an HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of admission to the hospital for delivery. Pregnant women at risk for HBV infection also should be vaccinated. To avoid misinterpreting a transient positive HBsAg result during the 21 days after vaccination, HBsAg testing should be performed before vaccine administration. All laboratories that conduct HBsAg tests should test initially reactive specimens with a licensed neutralizing confirmatory test. When pregnant women are tested for HBsAg at the time of admission for delivery, shortened testing protocols can be used, and initially reactive results should prompt expedited administration of immunoprophylaxis to neonates. Pregnant women who are HBsAg positive should be reported to the local or state health

department to ensure that they are entered into a case-management system and that timely and appropriate prophylaxis is provided to their infants. Information concerning the pregnant woman's HBsAg status should be provided to the hospital in which delivery is planned and to the health-care provider who will care for the newborn. In addition, household and sex contacts of women who are HBsAg positive should be vaccinated. Women who are HBsAg positive should be provided with, or referred for, appropriate counseling and medical management.

4. All pregnant women aged < 25 years and older women at increased risk for infection (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) should be routinely screened for Chlamydia trachomatis at the first prenatal visit. Women aged < 25 years and those at increased risk for chlamydia also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the neonate. Pregnant women found to have chlamydial infection should have a test-of-cure to document chlamydial eradication (preferably by NAAT) 3–4 weeks after treatment and then retested within 3 months. Screening during the first trimester might prevent the adverse effects of chlamydia during pregnancy, but evidence for such screening is lacking.

5. All pregnant women aged < 25 years and older women at increased risk for gonorrhea (those with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) should be screened for N. gonorrhoeae at the first prenatal visit. Additional risk factors for gonorrhea include inconsistent condom use among persons not in mutually monogamous relationships, previous or coexisting sexually transmitted infection, and exchanging sex for money or drugs. Clinicians should consider the communities they serve and might choose to consult local public health authorities for guidance on identifying groups that are at increased risk. Gonococcal infection, in particular, is concentrated in specific geographic locations and communities. Women found to have gonococcal infection should be treated immediately and retested within 3 months. Pregnant women who remain at high risk for gonococcal infection also should be retested during the third trimester to prevent maternal postnatal complications and gonococcal infection in the neonate.

6. All pregnant women at risk for HCV infection should be screened for hepatitis C antibodies at the first prenatal visit. The most important risk factor for HCV infection is past or current injection drug use. Additional Recommendations and Reports risk factors include having had a blood transfusion, receipt of an unregulated tattoo, having been on long-term hemodialysis, intranasal drug use, and other percutaneous exposures. No established treatment regimen exists for pregnant women infected with HCV. However, all women with HCV infection should receive appropriate counseling and supportive care as needed. No vaccine is available to prevent HCV transmission.

7. Pregnant women should undergo Papanicolau (Pap) test at the same frequency as nonpregnant women, although recommendations for management of abnormal Pap tests in pregnancy differ.

8. Evidence does not support routine screening for BV in asymptomatic pregnant women at high risk for preterm delivery. Symptomatic women should be evaluated and treated.

9. Evidence does not support routine screening for Trichomonas vaginalis in asymptomatic pregnant women. Women who report symptoms should be evaluated and treated appropriately.

10. Evidence does not support routine HSV-2 serologic screening among asymptomatic pregnant women. However, type-specific serologic tests might be useful for identifying pregnant women at risk for HSV infection and guiding counseling regarding the risk for acquiring genital herpes during pregnancy. In the absence of lesions during the third trimester, routine serial cultures for HSV are not indicated for women in the third trimester who have a history of recurrent genital herpes.

11. For a more detailed discussion of STD screening and treatment among pregnant women, refer to the following references: Screening for HIV in Pregnant Women: Systematic Review to Update the 2005 U.S. Preventive Services Task Force Recommendation; Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement; ACOG/ AAP Guidelines for Perinatal Care; Rapid HIV Antibody Testing During Labor and Delivery for Women of Unknown HIV Status: A Practical Guide and Model Protocol; Viral Hepatitis in Pregnancy; Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States - Recommendations of the Immunization Practices Advisory Committee (ACIP); Screening for Chlamydia and Gonorrhea: U.S. Preventive Services Task Force Recommendation Statement; Canadian guidelines on sexually transmitted infections; USPSTF recommendations for STI screening; and Screening for Bacterial Vaginosis in Pregnancy to Prevent Preterm Delivery: U.S. Preventive Services Task Force Recommendation Statement.

12. Information regarding HIV infection, testing, transmission, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents and young adults as part of health care.

13. Health-care providers who care for adolescents and young adults should integrate sexuality education into clinical practice. Providers should counsel adolescents about the sexual behaviors that are associated with risk for acquiring STDs and educate patients regarding evidence-based prevention strategies, all of which include a discussion about abstinence and other risk-reduction behaviors (e.g., consistent and correct condom use and reduction in the number of sex partners).

2. VIRAL INFECTIONS

A variety of viruses may adversely affect the fetus when they infect a pregnant woman (Table 1). Adverse effects may include increased maternal morbidity or mortality, fetal loss (abortion, stillbirth), congenital infections, fetal growth restriction, and prematurity. Of special importance because of their detrimental effects are human immunodeficiency virus, parvovirus B19, and rubella.

Table 1 — Viral Diseases Transmitted from Mother to Child Transplacentally

Disease	Risk to mother	Risk to fetus	Clinical Findings	Maternal	Fetus/ neonate	Therapy
CMV	Minimal except in immunocompromised patient	Severe fetal injury with primary maternal infection transmitted antepartum	Flu-like illness with diffuse lymphadenopathy	Serology	Amniocentesis-viral culture; ultrasound	Supportive
Hepatitis B	Acute infection hepatitis; chronic infection cirrhosis	Perinatal transmission of infection	Acute infection hepatitis; chronic infection liver failure	Serology (HBsAg)	Serology (HBsAg)	
Hepatitis C	Acute infection hepatitis; chronic infection cirrhosis	Perinatal transmission of infection	Acute infection hepatitis; chronic infection liver failure	Serology (Anti-HBC)	Serology (Anti-HBC)	
Hepatitis D	Coinfection with hepatitis B increases the risk for chronic liver disease	Perinatal transmission of infection	Acute infection hepatitis; chronic infection liver failure	Serology (Anti-HBD)	Serology (Anti-HBD)	Supportive
Hepatitis E	Severe acute infection with 10–20 % mortality	Fetal death resulting from maternal death. Perinatal transmission of infection rare	Acute infection hepatitis	Serology (Anti-HBE)	Serology (Anti-HBE)	Supportive
Herpes simplex	Minimal except in immunocompromised patient	Severe neonatal infection when delivered to mother with primary infection	Vesicular eruption on genital mucosa	Clinical examination; culture of lesions; PCR	Clinical examination; culture of lesions; PCR	Antiviral (acyclovir, famciclovir, valacyclovir)

Disease	Risk to mother	Risk to fetus	Clinical Findings	Maternal	Fetus/ neonate	Therapy
Parvovirus B19	Aplastic crisis (hemoglobinopathy present)	Hydrops fetalis; neurologic and hematologic sequelae in neonate are rare	Rash (slapped cheeks), fever, arthralgias	Serology	Serology	Supportive
HIV	Severe disease; opportunistic infections	Prenatal, perinatal, or postnatal transmission of infection	Lymphadenopathy, wasting, opportunistic infection	Serology	Serology	Antivirals
Rubella	Minimal	Congenital rubella syndrome (greates risk in first trimester)	Rash, fever	Clinical examination; serology	Ultrasound	Supportive
Rubeola	Rarely pneumonia or encephalitis	Minimal risk of teratogenicity	Rash, fever, pneumonia	Clinical examination; serology	—	Supportive
Varicella	Occasionally pneumonia and encephalitis	Varicella congenital syndrome 2 %	Rash, fever	Clinical examination; Tzanck test; culture of vesicle	Ultrasound	VZIG for postexposure prophylaxis; antiviral (acyclovir, famciclovir, valacyclovir)

2.1. VIRAL HEPATITIS

Three types of viral hepatitis (A, B, and C) affect females of all ages. The incidence is 0.2 % in pregnancy when manifestations, although similar, may be more severe and prolonged (especially in advanced pregnancy). Maternal and perinatal prognosis is quite different in the three types. Treatment for all three generally consists of supportive medical measures as for the non-pregnant patient. Operative intervention is to be avoided, if possible. Anesthetics, analgesics, and sedatives that may be hepatotoxic must be avoided. A very low prothrombin concentration may lead to hemorrhage, which should be treated with oral or parenteral vitamin K. The maternal and fetal risks are low (except as noted later) if adequate nutrition is maintained. Terminate pregnancy only in case of impending or actual hepatic coma. Deterioration may justify cesarean section for the viable infant. If obstetric care is

good, the maternal mortality rate is approximately that of non-pregnant women with viral hepatitis. It is wise to allow more than 1 year to elapse between hepatitis and subsequent pregnancy. By this time, liver function tests should return to normal values unless serious complications have developed. The fetal effect of chronic active hepatitis depends on the extent of maternal disease (loss is high with poor liver function or esophageal varices).

Viral hepatitis is the commonest cause of jaundice in pregnancy in the tropics. Hepatitis is mostly restricted to the illnourished mothers, living in unhygienic environment. In the tropics, it often occurs as an epidemic form. There is also increased incidence of its affection in the pregnant state compared to the non-pregnant one. At present six distinct types of highly contagious hepatitis virus have been identified. Each type has different clinical effect to the pregnant women and her fetus. Treatment with immunosuppressants and corticosteroids does not preclude pregnancy.

2.1.1. Hepatitis A (HAV)

Infection is spread by faecal-oral route. Hepatitis A is usually quite benign during pregnancy, with only enteric isolation, supportive treatment, and careful monitoring of liver enzymes being necessary. Diagnosis is confirmed by detection of IgM antibody to hepatitis A. Disease is usually self-limited and fulminant hepatitis is rare. Perinatal transmission is rare, chronic carrier state does not exist. The virus is not teratogenic. Pregnant woman exposed to HAV infection should receive immunoglobulin 0.02 mL/kg within 2 weeks of exposure. She should also have hepatitis A vaccine single dose 0.06 mL IM. It is safe in pregnancy.

2.1.2. Hepatitis B (HBV)

Etiology/Pathogenesis. It is a global public health problem. Hepatitis B (serum hepatitis) occurs in about 1:500 pregnancies. The virus is transmitted by parenteral route, sexual contact, vertical transmission and also through breast milk. Vertical transmission may be prevented by hepatitis B immune globulin and hepatitis B vaccine. The maternal course is unaltered, but prematurity is increased. Care must be taken not to infect the newborn at delivery. When the mother is HBsAg positive and HBsAb negative, the neonate should have HBsAg and HBsAb studies drawn and receive both hepatitis B immune globulin and the hepatitis B vaccine immediately. If antigenicity studies can be obtained rapidly, hepatitis B vaccine may be delayed up to 7 days of age. If the baby is HBsAg negative, the original dose is given and is then repeated 1 month later. The third dose is given 6 months after the original dose.

Clinical manifistation. The acute infection is manifested by flu like illness as malaise, anorexia, nausea and vomiting. There may be arthralgia and skin rash. In majority, it remains asymptomatic. Jaundice is rare and fever is uncom-

mon. Clinical course (HBV): Nearly 90–95 % of patients clear the infection and have full recovery. 1 % develop fulminant hepatitis resulting massive hepatic necrosis. 10–15 % become chronic and 10 % of these chronic cases suffer from chronic active hepatitis, cirrhosis and hepatocellular carcinoma. Diagnosis is confirmed by serological detection of HBsAg, HBeAg, (denote high infectivity) and antibody to hepatitis B core antigen (HBcAg) and HBV DNA titer. Chronic carriers are diagnosed by presence of HBsAg or HBeAg and Anti HBc antibody 6 months after the initial infection. Liver enzymes are elevated during the initial phase.

Fetal/neonatal complications. HBV is not teratogenic. The risk of transmission to fetus ranges from 10 % in first trimester to as high as 90% in third trimester and it is specially high (90 %) from those mothers who are seropositive to hepatitis B surface antigen (HBsAg) and e-antigen (HB eAg). Neonatal transmission mainly occurs at or around the time of birth through mixing of maternal blood and genital secretions. Approximately 25 % of the carrier neonate will die from cirrhosis or hepatic carcinoma, between late childhood to early adulthood.

Diagnosis. All pregnant women should be screened for HBV infection at first antenatal visit and it should be repeated during the third trimester for 'high risk' groups. Detection is by screening with hepatitis B surface antigen (HBsAg) and the hepatitis B surface antibody (HBsAb). HBsAb indicates a noninfectious state. HBsAg without HBsAb is the chronic carrier state, with a high likelihood (75–95 %) of vertical transmission. When HBsAg is detected, it is imperative to ascertain if the e antigen is present.

Management. There is no specific treatment for viral hepatitis. It is generally supportive.

1. Rest: The patient should be put to bed rest, if necessary by hospitalization.

2. Isolation: The patient should be kept in isolation. Blood samples are to be collected with gloved hand. Disposable syringes should be used. The excreta is to be disposed carefully.

3. Nutrition: Diet rich in carbohydrate and adequate protein is to be prescribed. Initially, glucose drink, fruit juice may be given. Dietary fat restriction is not necessary. If the patient cannot tolerate oral feeding, 10% glucose may be given intravenously.

4. Drugs: To prevent formation of the toxic nitrogenous compound from the bacterial flora of the gut, oral neomycin (1 gm to be given 6 hourly) is helpful. Lactulose (15–30 mL three times daily), reduces colonic ammonia absorption and it acts as an osmotic laxative. Hepatotoxic drugs should not be used. There is no place for termination of pregnancy.

5. Prevention of complications: Hypokalemia, hypoglycemia and hypocalcemia are corrected by regular blood checkup. Hemorrhagic complications are managed by giving blood or fresh frozen plasma.

Obstetrics management. HBV infection can be prevented by vaccination and the recombinant vaccine is safe in pregnancy. Pregnant woman who is seronegative, should have HB immunoglobulin (HBIG), 0.06 mL/kg IM, soon following exposure and a second dose after 1 month. Then she should be given recombinant DNA vaccine intramuscularly 1 mL, 3 doses at 0, 1 and 6 months. All infants born to HBsAg positive mothers should have HBIG 0.5 mL IM within 12 hours of birth. Active immunization with HB vaccine (0.5 mL) is also given IM at a separate site at the same time schedule. This is very effective (85–95 %) to protect the infant from HBV infection. Breastfeeding is not contraindicated. Similar to HIV, perinatal transmission of HBV depends on maternal viral load. Lamivudine and HBIG are effective to reduce the transplacental transmission of HBV to the fetus. Lamivudine is given 150 mg/day from 34 weeks. Health care workers should receive hepatitis B vaccine and they should avoid needle stick injury and blood to blood contact. During labor: Hepatotoxic drugs should be avoided; to administer vitamin K, 5 mg intramuscularly to raise the prothrombin level; prophylactic oxytocin is to be given.

Prevention. Improvement in sanitation, supply of safe drinking water and adequate care of personal hygiene are the essential prerequisites. Use of disposable syringe or boiling of syringe prior to use are the positive steps in prevention. Screening of blood donors for HBs Ag should be routinely done.

2.1.3. Hepatitis C (HCV)

Etiology/Pathogenesis. It is recognized as the major cause of non-A, non-B hepatitis. Transmission is mainly blood borne and to a lesser extent by faecal-oral route. It is responsible for chronic active hepatitis and hepatic failure. Hepatitis C virus (HCV) currently infects 2 % of the U.S. population, making it the most common chronic blood borne infection. About 40 % of chronic liver disease is HCV related, and HCV is estimated to cause 8000–10,000 deaths per year in the United States. End-stage liver disease caused by HCV is the most common current indication for liver transplantation in the United States. Moreover, because HCV currently is 3-fold higher among those 30–49 years old, the health care burden as well as deaths from HCV related liver disease will increase as much as 4-fold over the next 10–20 years. Most HCV infections are acquired by direct percutaneous exposure to blood. Known acquisitions account for 90 % of all HCV infections: intravenous drug use (60 %), sexual exposure (20 %), known exposures (occupational, hemodialysis, household, perinatal — 10 %). The remaining 10 % of individuals with HCV have no demonstrable source of infection, but the majority are of low socioeconomic status (a risk factor). In recent studies, up to 77 % of intravenous drug users have HCV infections.

Clinical manifistation. Acute HCV infection has been thought to progress to chronic hepatitis in 85 % of cases. However, recent studies indicate that healthy individuals who become HCV infected are at less risk for progressive

liver disease than previously thought. Thus, although chronic hepatitis C increases risk for cirrhosis and hepatocellulararcinoma, there is controversy about the amount of risk and the time required for this progression. Current best estimates are that 20–30 % of infected individuals will develop fibrosis and cirrhosis. Of those with fibrosis and cirrhosis, 20 % will progress to liver decompensation and 10–20 % to hepatocellular carcinoma. The time required for the progression is 20–30 years. Risks of enhancing the progression include: alcohol intake, male sex, age 40 years at infection, and coinfection with HIV or hepatitis B virus. Although sexual transmission of HCV occurs, to what extent is unknown. The literature suggests: HCV presence in seminal fluid, HCV presence in vaginal secretions, a higher rate of HCV infections in the sexually promiscuous (2–12 %), and molecular biologic evidence of sexual transmission. Confounding evidence is that monogamous sexual partners of HCV infected individuals have a low rate (2.5 %) of interspousal transmission despite long duration of sexual exposure. Thus, the use of condoms is currently only recommended in cases of multiple partners and for those at high risk of transmission.

Maternal complications. Pregnancy is not contraindicated in women infected with HCV. Most who develop chronic HCV infections not be aware that they have been infected, for the onset is so mild. The chronic infection is asymptomatic and the duration of the disease is prolonged. Although the personal objects (razors, tooth-brushes, nail clippers) of an HCV infected person should not be shared, eating utensils have not been incriminated in infections.

Fetal/neonatal complications. Perinatal transmission (10–40 %) is high when coinfected with HIV and HBV. Mother to infant transmission is restricted to infants whose mothers are viremic. If the mother is coinfected with HIV, the rate is higher. This infection occurs predominantly during or near delivery, and no treatment or delivery method (such as caesarian section) has been demonstrated to decrease this risk. HCV has not been shown to be transmitted through breast milk, although mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding.

Diagnosis. Routine screening for HCV infection is not recommended for all pregnant women. Detection is by antibody to HCV by EIA, which develops usually late in the infection. Confirmation is done by recombinant immunoblot assay (RIBA-3). Pregnant women with a known risk factor for HCV infection should be offered screening. Infants born to mothers with HCV infection should be tested for HCV infection; because maternal antibody is present for the first 18 months of life and before the infant mounts an immunologic response, nucleic acid testing is recommended.

Management. Interferon for 12 months is the current standard therapy for individuals with chronic HCV and elevated ALT levels, but rates of sustained virologic response are only 15–20 %. However, combination therapy (alpha interferon and ribavirin) is emerging as more efficacious, and therapy is rapidly evolving.

Obstetrics management. Currently, there is no data to indicate that the rate of perinatal HCV infection is influenced by the mode of delivery or by breast feeding. Breastfeeding is not contraindicated.

Prevention. No effective vaccine against HCV is available. Sexual partners should be tested for anti-HCV. HCV positive individuals should not donate blood, organs, or tissue. HCV patients with active disease should refrain from alcohol.

2.1.4. Hepatitis D (HDV), E(HEV)

Etiology/Pathogenesis. Hepatitis D is seen in patients infected with HBV either as a co-infection or super infection. Perinatal transmission is known. Chronic carrier state is seen. Neonatal immunoprophylaxis for HBV is almost effective against HDV. Fulminant course and maternal mortality (2–20 %) are high.

Hepatitis E virus is a small, nonenveloped RNA virus spread via the fecal-oral route usually through contaminated water. There is no evidence of parenteral or sexual transmission. Person-to-person transmission is unusual. HEV is responsible for large epidemics (attack rates of 1 to 15 percent) of acute hepatitis in southeast and central Asia, the Middle East, parts of Africa, and Mexico. Sporadic HEV in these areas may account for 50 to 70 percent of sporadic viral hepatitis. In other parts of the world, HEV infection is infrequent and is restricted predominantly to persons who have traveled to endemic areas. Outbreaks of HEV have been characterized by a high attack rate among pregnant women, especially among women in the second or third trimester.

Clinical manifistation. HEV generally causes an acute icteric hepatitis; chronic infection has not been observed. It may lead to fulminant hepatitis.

Maternal complications. There is increased incidence of postpartum hemorrhage, hepatic coma, renal failure, coagulopathy, infection and hepatorenal syndrome. All these lead to increased maternal morbidity and mortality. Medical termination of pregnancy does not alter the prognosis of the patient. Mortality rates for pregnant women have ranged from 10 percent to as high as 25 percent.

Fetal/neonatal complications. Mother-to-newborn (transplacental) transmission may occur. Reports indicate that abortion, death of the fetus *in utero*, premature delivery, or death of the baby soon after birth are seen in women with icteric hepatitis or with fulminant hepatic failure induced by HEV. There is increased incidence of abortion, preterm birth and intrauterine death leading to increased fetal wastage. Congenital malformation of the fetus following viral hepatitis in early pregnancy is inconclusive. Perinatal mortality is about 20–70 %.

Diagnosis. The disease is diagnosed serologically. ELISA can detect HEV specific IgG and IgM antibodies.

Management. Only symptomatic therapy is available for HEV infection; no vaccine is presently available. Low-dose immune serum globulin does not prevent infection. Prevention therefore relies on ensuring a safe drinking water supply.

Prognosis: Fulminant hepatitis is more common in hepatitis E, less common in hepatitis C and rare in hepatitis A. Mortality is very high in fulminant type.

2.2. HERPES SIMPLEX VIRUS INFECTION (HSV)

Etiology/Pathogenesis. HSV infection is ubiquitous. Among HSV infections, genital herpes is widely prevalent, affecting at least 50 million Americans. This disease affecting about 1:4000 (1:1700–50,000) gravidas is the most common skin disorder that affects the fetus. The cause of herpes gestation is unknown, but it may be a variation of dermatitis herpetiformis. It is not related to the herpesvirus, and the nomenclature is unfortunate. The intensely burning, pruritic, occasionally painful urticarial papulovesicular eruption involving the buttocks, extensor surfaces of the arms and legs, back, and upper abdomen begins during or after the fifth month of pregnancy. Occasionally, it is noted early postpartum. Fetal death may occur during any period. The fatal pathophysiologic sequence is unexplained.

Seropositivity to type 1 HSV (HSV-1) is acquired by a majority of people by the age of 7 years. The incidence of seropositivity to HSV-2 varies with age, sexual habits, and economic status. HSV-1 is the serotype most often found in oral lesions, while HSV-2 causes most lesions below the waist. The prevalence of HSV-2 infections in the US is rising, with approximately 1.6 million new infections acquired annually. Among adults, 5–10 % have a history of symptomatic genital HSV-2 infection. However, another 20–30 % who have never had symptomatic genital infection demonstrate type-specific antibodies against glycoprotein G (gG) of the HSV-2 virion. Thus, because HSV-2 infections rarely cause ulcerative lesions, most HSV-2-seropositive individuals are unaware of their exposure. Clearly then, much must be done toward prevention. There are three primary types of genital herpes syndromes. Primary infection occurs with initial infection with either HSV-1 or -2 and without prior exposure to either. Recurrent infection is due to reactivation of latent virus, and is therefore not a reinfection. Finally, nonprimary first-episode genital herpes occurs when a patient has had a prior exposure to the other viral serotype.

Transmission of genital HSV requires intimate contact of infectious secretions with susceptible mucous membranes or skin. Mechanical friction provides for more efficient transfer. Unfortunately, clinical history does not provide reliable information regarding the likelihood of sexual transmission. Although analysis of the survival characteristics of the herpes simplex virion in water and on plastic surfaces supports the possibility of fomite transfer, there are no documented cases of such transmission. Essentially all cases of genital herpes are spread via sexual contact; genital HSV-1 is usually due to oral-genital contact. Transmission to the fetus or neonate can occur antenatally, intrapartum, or postnatally. The highest risk is at the time of delivery, responsible for 85 % of all neonatal herpes cases. Intrauterine infection, resulting mainly from transplacental passage or ascension via the cervix, accounts for 5–8 % of cases. Intrapartum transmission is not necessarily dependent upon maternal symptoms, but rather

upon maternal viral shedding, especially when that shedding occurs in the context of first-episode genital herpes as opposed to reactivation disease. The risk of intrapartum transmission with a vaginal delivery in HSV-2-seropositive, asymptomatic women is 0.02 %, with symptomatic recurrence it is 1–3 %, and with asymptomatic seroconversion, i.e., with primary infection, or with non-primary first episode near the time of delivery it is 40 %.

Genital tract infection is due to HSV-2. Infection may be primary, nonprimary, first episode and recurrent. It is transmitted by sexual contact. Primary infection may occur during pregnancy. Reactivation or recurrent infection occurs resulting in virus shedding with or without symptomatic lesions. HSV-1 infection is usually herpes simplex labialis.

Clinical manifistation. Increased risk of abortion is inconclusive. If the primary infection is acquired in the last trimester there is chance of premature labor or IUGR. Transplacental infection is not usual. The fetus becomes affected by virus shed from the cervix or lower genital tract during vaginal delivery. The baby may be affected in utero from the contaminated liquor following rupture of the membranes. Risk of fetal infection is high in primary genital HSV at term due to high virus shedding compared to a recurrent infection. Cesarean delivery is indicated (ACOG) in an active primary genital HSV infection where the membranes are intact or recently ruptured.

Herpes simplex virus (HSV) is a double-stranded DNA virus, primarily of two subtypes (1 and 2), that is responsible for a variety of infections involving mucocutaneous surfaces, the central nervous system (CNS), and visceral organs. Taking up residence in sensory neuronal ganglia, genital HSV infection is a recurrent, lifelong infection. Systemic symptoms are more common in primary occurrences, and can include fever, malaise, myalgia, and headache. Local symptoms include pain, discharge, adenopathy, dysuria, and urinary retention secondary to pain or local nerve involvement. Painful vesicles, which may emerge 2-10 days following primary exposure, ulcerate and heal without scarring. Viral shedding persists until the lesions heal. Cervical shedding is present with primary infection in more than 80 % of patients and in up to 30 % of recurrences. Asymptomatic shedding occurs in 0.35–1.4 % of pregnancies. Genital HSV infection can lead to a number of complications that can profoundly affect the developing fetus and/or the neonate.

Grouped vesicles on inflammatory bases are typical. The bullae of herpes gestation is form an annular pattern around the edge of the lesions, in contrast to those of erythema multiforme, which has bullae that are centrally located. The lesions leave small pigmented scars on healing. A high eosinophil count in blood and vesical fluid is usual. Biopsy shows subepidermal bullae, increased eosinophils, and deposits of complement in the basement layer of the skin with immunofluorescent staining. Herpes gestation is marked by a complement fixing HG factor in the serum. Herpes gestation tends to recur with subsequent preg-

nancies, but the extent of the recurrence is not related to the extent of the disease in the index case. There is a genetic predisposition to herpes gestationis and the disease appears to be mediated by an IgG specific for a 180-kD component of hemidesmosomes. The maternal prognosis is good, with the process usually abating in the non-pregnant state. Perinatal outcomes are less well understood, with reports variously ranging from minimal risk to intrauterine growth retardation or perinatal death. An occasional newborn of an affected mother may manifest herpes gestationis lesions. Some authorities believe the skin manifestions are merely a reflection of a primary immunologic event taking place in the placenta. The differential diagnosis of bullous lesions includes nonimmune as well as autoimmune lesions. Nonimmune causes of similar lesions include: contact dermatitis, bullous reactions to drugs or insect bites, and infections. Autoimmune mucocutaneous bullous (blistering) diseases includes herpes gestationis, toxic epidermal necrolysis, and erythema multiforme. Crucial elements in distinguishing among the potential causes are morphology and lesions distribution, presence or absence of mucosal lesions, and scarring. Corticosteroids are useful but not curative.

Maternal complications. Perinatal transmission has been linked with spontaneous abortion, preterm labor, and congenital malformations. Anomalies linked to HSV are similar to those seen with congenital cytomegalovirus (CMV) infection: microcephaly, periventricular calcifications, chorioretinitis, intrauterine growth restriction, and vesicular eruptions.

Fetal/neonatal complications. While evidence for the teratogenic potential of HSV is circumstantial, neonatal disease can be devastating. This can range from infection of the skin, eyes and mouth, which, though rarely fatal, can lead to neurologic impairment in 30% of affected children, to CNS infection (symptoms include seizures, poor feeding, and irritability; mortality is more than 50% if untreated), and disseminated infection, which is often complicated by encephalitis and can be fatal in over 80 % of cases if left untreated, with neurologic impairment in nearly all survivors.

Neonatal infection may be disseminated (fatal) or localized or it may be asymptomatic. Diagnosis is made by detection of the viral DNA by PCR. It is manifested as chorioretinitis, microcephaly, mental retardation, seizures and deaths. Neonatal HSV infection is treated with intravenous acyclovir. Neonatal mortality is high. Prophylactic acyclovir (400 mg twice daily) is appropriate for women with recurrent infections particularly near term. Breastfeeding is allowed provided the mother avoids any contact between her lesions, her hands and the baby.

Diagnosis. Diagnosis can be made by viral culture, Pap smear, monoclonal antibody testing, ELISA or PCR. Cultures are widely used in persons with ulcers, but sensitivity declines within a few days of ulcer occurrence. PCR testing is highly sensitive. Pap smear findings indicating disease are usually incidental, and should not serve as a primary diagnostic modality.

Monoclonal antibody and ELISA testing have limited sensitivity in the absence of lesions and do not allow for the distinguishing of HSV type. Serologic diagnosis with Western blotting of gG can identify types 1 and 2. Food and Drug Administration (FDA)-approved commercially available gG-based type-specific assays for HSV have sensitivities ranging from 80% to 98%, with specificity ≥ 96 %.

Management. Acyclovir 400 mg three times daily for five days is the drug of choice when virus culture is positive.

Obstetrics management. Oral suppressive therapy with the antiviral agent acyclovir in primary infection has been shown to decrease duration of shedding, pain, new lesion formation, and time to complete healing. Duration of shedding may be decreased by 80 %. Oral acyclovir is also effective in suppressing recurrences with long-term use. Furthermore, among 601 acyclovir-exposed pregnancies (425 in the first trimester), there was no notable increase in the rate of birth defects compared with background, and there was no notable pattern of anomalies. In a systematic review of acyclovir prophylaxis administered in five different trials that included women with first-episode disease, recurrent disease, and all HSV disease, Sheffield et al. were able to demonstrate that prophylactic use of acyclovir starting at 36 weeks' gestation reduced the rate of clinical recurrence at delivery, the rate of Cesarean delivery for HSV, the overall Cesarean delivery rate, and the rate of asymptomatic HSV shedding. Thus, acyclovir (or, alternatively, famcyclovir or valacyclovir) suppressive therapy starting at 36 weeks' gestation should be considered in genital HSV patients, especially those with first-episode disease occurring during pregnancy, as there may not be adequate time for the generation of homologous maternal IgG antibodies that seem to protect the neonate from congenital acquisition of disease.

In the largest prospective study of its kind, Brown et al. looked at over 58000 women in the state of Washington who underwent collection of genital secretions for HSV culture at the time of their presentation in labor. None of these women received or were receiving suppressive viral therapy. Of these women, 202 had HSV-positive cultures. Fifty-eight percent of these women were delivered vaginally, and 42 % were delivered via Cesarean section, with 71 % of the latter having recognized genital lesions as the indication for surgical delivery. Although not quite reaching statistical significance, the odds ratio (OR) for neonatal HSV infection was 0.14 (95 % CI, 0.02–1.08), tending towards favoring Cesarean delivery. Based on previous studies, and the lack of a randomized, prospective, controlled trial to evaluate Cesarean delivery versus vaginal delivery even in the case of active genital lesions, the American College of Obstetricians and Gynecologists, in a 1999 Practice Bulletin, recommended Cesarean delivery in women "with active genital lesions or symptoms of vulvar pain or burning, which may indicate an impending outbreak," but did not recommend such a delivery modality in cases of recurrent disease with lesions distant from

the perineum (such as the buttocks or the thigh). Brown et al. also found a statistically significant increase of nearly sevenfold for the development of neonatal HSV with the use of invasive fetal monitoring intrapartum. It is recommended that these monitors be avoided if possible, as should rupture of the membranes more than 4–6h prior to delivery. Based on this finding, forceps and vacuum-assisted delivery should also be minimized. All these recommendations should of course be mitigated by concerns for fetal safety, and thus decisions should be made that are appropriate for the clinical situation at hand.

Preventions. While adult genital HSV is problematic, transmission to the fetus or neonate can be far more tragic. Prevention of transmission to the fetus, and especially the neonate, is an important goal. Efforts toward this goal include recognition of lesions, elective Cesarean delivery, suppression of viral shedding during the peripartum period, and maintenance of neonatal skin integrity.

2.3. CYTOMEGALOVIRUS INFECTION (CMV)

Etiology/Pathogenesis. An estimated 0.2–2.2 % of all neonates are infected in utero, with only 5–10 % of these infants symptomatic at birth. Affecting approximately 1 in 40000 liveborn infants in the United States annually, CMV causes 30000–40000 cases of congenital infection every year. Primary CMV infection occurs in 1–2 % of pregnant women; it is estimated that about 50 % of reproductive-age women are susceptible to CMV infection. The rate of seropositivity, the risk of congenital infection, and the incidence of recurrent infection are greater in women of lower socioeconomic status. CMV infection is spread through infected secretions or body fluids such as endocervical mucus, semen, blood, urine, saliva, breast milk, and tears. High-risk environments for exposure to CMV include childcare centers, newborn nurseries, renal dialysis units, and areas of hospitals providing care for immunocompromised individuals.

It is a DNA virus. Transmission may be sexual, respiratory droplet or transplacental. Virus is also excreted with urine, cervix and breast milk. Fetus is affected by transplacental route in about 30–40 % cases. Chorioretinitis, periventricular necrosis with calcification, microcephaly, and sclerosis of the bones are often noted at birth. Early jaundice beginning on the first or second day, melena, hematemesis, and hematuria develop. The antemortem diagnosis can be made by identification of cytomegalic inclusion cells in the gastric washings, cerebrospinal fluid, or fresh urine. Culture of CMV is proof of the diagnosis. The direct and indirect serum bilirubin are elevated, but the Coombs' test is negative. Death may occur soon after birth as a result of interstitial pneumonitis, focal hepatitis, or adrenocortical failure. There is no cure. Corticosteroids and supportive therapy together with immune serum globulin may be helpful. When the obviously infected infant survives, marked developmental and psychomotor deficiencies

and hepatosplenomegaly usually are present. Hearing loss is frequent in the more numerous cases of clinically inapparent CMV.

Cytomegalovirus (CMV) is a double-stranded DNA herpesvirus transmitted by contact with infected blood, saliva, urine, breast milk, or through sexual contact. The mean incubation period is 40 days (range, 28–60 days). Although a brief, self-limited, flu-like illness with fever, chills, malaise, myalgia with leukocytosis, and elevated liver function tests may be experienced, the majority of infected adults are with more severe fetal neurologic morbidity following primary infections. Cytomegalovirus is the most common congenital infection, occurring in 0.2 to 2.2 % of all neonates, and is the leading cause of congenital hearing loss. Prenatally, CMV infection can be suspected following a documented maternal primary infection or suggestive ultrasound findings; these include abdominal, liver, and lateral cerebrospinal fluid (CSF) ventricle calcifications, ventriculomegaly, hydrops fetalis, echogenic bowel, ascites, and hepatosplenomegaly. Structural anomalies, especially within the central nervous system, dictate a much poorer fetal prognosis. Diagnostic confirmation can usually be made through detection of CMV in amniotic fluid by culture or PCR. Fetal blood sampling for antibody response is less sensitive due to the immaturity of the fetal immune system and alterations of platelet count and liver function tests are nonspecific. Although most infants with congenital CMV are asymptomatic at birth, evidence of the aforementioned ultrasound findings, as well as growth restriction, jaundice, petechiae, and thrombocytopenia, may be observed. No therapies are currently available for maternal or fetal CMV infection, and thus routine serologic screening for CMV during pregnancy is not recommended. Although the antiretroviral therapies ganciclovir or foscarnet have been used for CMV retinitis in AIDS patients, the use of ganciclovir in combination with CMV hyperimmune gamma globulin in CMV-infected neonates has not been shown to prevent long-term neurologic sequelae. A vaccine is under development but remains currently unavailable. Patient education efforts thus should focus on preventative measures, including careful handling of potentially infected articles (such as diapers) and thorough handwashing when around young children or immunocompromised individuals. In addition, avoidance of high-risk behaviors such as intravenous drug use and sharing of needles should be emphasized when appropriate. Barrier contraception should be encouraged as a method of contraception.

Human cytomegalovirus (CMV), otherwise known as human herpes virus 5 (HHV-5), is an enveloped double-stranded DNA virus and a member of the Herpesviridae family. CMV-specific IgG and IgM antibodies may be detectable several weeks after infection. Many different strains of CMV have been identified by restriction endonuclease analysis. Owing to its ubiquity, CMV is the most common viral cause of intrauterine and congenital infection as well as of

sensorineural deafness. Unfortunately, CMV can be spread to the fetus with either primary infection or reactivation disease and, in most instances, with the mother remaining asymptomatic.

Fetal infection can occur with both primary and recurrent maternal infection; however, the likelihood and severity of congenital disease is greater with a primary infection. Transmission to the fetus occurs in approximately 20–50 % of pregnancies with primary maternal CMV infection. Congenital infection can occur as a result of recurrent maternal infection, but the risk is less (approximately 1 % detected in the newborn period and up to 8 % if followed for 5 years) and the manifestations milder (mainly hearing loss). Transmission can occur at any time during pregnancy, with the lowest risk of transmission associated with primary CMV acquired periconceptionally, and an equal risk of transmission in the first and second trimesters; the third trimester poses the greatest risk of vertical transmission. However, there is evidence to indicate that fetuses that acquire infection earlier in gestation are at higher risk for worse outcomes compared with infection acquired later in gestation. Studies indicate that recurrent infections and transmission to the fetus in immune women are more frequently due to reactivation than to reinfection.

Clinical manifistation. CMV infection in the immunocompetent mother is usually asymptomatic. In some patients, a heterophile-negative mononucleosis-like syndrome may be present. Fever, malaise, myalgias, mild pharyngitis, minimal lymphadenopathy, lymphocytosis, and abnormal liver function test results may be present in such cases.

Most cases of cytomegalovirus infection disease are clinically inapparent. In some adults, the symptoms are like those of infectious mononucleosis. The disease may be sexually transmitted. During pregnancy, the only sign may be mild leukorrhea. Specific virus-neutralizing and complement-fixing antibody reactions indicate that most women have (at some time) sustained this infection. About 20 % of adults do not have neutralizing antibody to cytomegalovirus and thus are considered susceptible for acute infections. There is now evidence that CMV is much more prevalent during pregnancy than was thought and causes severe anomalies in 10,000 infants in the United States per year. CMV is recovered from 15–20 % of women examined in public health clinics and from the semen of men who have had numerous sexual partners. The virus can be cultivated from the salivary glands of 10–25 % of healthy individuals, from the cervix of 10 % of healthy women, from the urine of 1 % of all newborns, and sometimes from breast milk. This carrier state probably explains subsequent cases occurring in the same family. Cytomegalovirus disease is usually acquired by the fetus during early intrauterine life. In the newborn, the disease produces erythroblastosis and thrombocytopenia that lead to scattered hemorrhages.

Maternal complications. The consequences of infection include abortion, stillbirth, IUGR, microcephaly, intracranial calcification, hepatosplenomegaly, thrombocytopenia, choroidoretinitis, mental retardation and deafness.

CMV infection is now the most common perinatal infection in both the UK and USA. The most serious manifestations associated with primary maternal infection include:

• Stillbirth.
• Hepatosplenomegaly and jaundice.
• Thrombocytopenia.
• Microcephaly.
• Chorioretinitis.

CMV may be acquired:

• In childhood from other children's saliva, tears, urine or stool.
•As an adult by sexual contact or blood transfusions.
• In the perinatal period by direct transmission across the placenta.

Fetal/neonatal complications. Unlike rubella, CMV may damage fetal organs throughout gestation. Amongst all infected fetuses only 10 % will suffer serious damage.

Congenitally-affected infants may excrete virus (through urine and nasopharynx) for up to 5–7 years. Infection is confirmed by viral culture of urine and nasopharyngeal secretions. CMV specific IgM is present with 80 % infected infants. Prenatal diagnosis by amniocentesis is possible using PCR to detect CMV DNA. Routine screening for all pregnant women is not cost effective. To date there is no vaccine, available for CMV.

Major target organ systems include the hematopoietic and central nervous systems and general development. Characteristics of fetal infection that may aid in prenatal diagnosis include intrauterine growth retardation, cerebral ventriculomegaly, ascites, microcephaly, hydrocephaly, periventricular calcifications, hepatosplenomegaly, cardiomegaly, hyperechogenic bowel, and oligo- or polyhydramnios. CMV may cause nonimmune hydrops. CMV has also been implicated in myocarditis; there have been reports of fetal heart block and of fetal supraventricular tachycardia. Ultrasound visualization of periventricular calcifications due to CMV has been reported, even in the second trimester.

Approximately 10 % of infants with congenital infection are symptomatic at birth. From the CDC registry, the most common clinical findings of congenital infection are hematologic (petechiae/purpura, 54 %; hepatosplenomegaly, 40 %; jaundice, 38 %; hemolytic anemia, 11 %), neurologic (intracranial calcifications, 37 %; microcephaly, 36 %; hearing impairment, 25 %; chorioretinitis, 11 %; seizures, 11 %; one or more neurologic findings, 68 %), small for gestational age (47 %), pneumonia (8 %), and death (9 %). Approximately 5–15 % of the initially asymptomatic infants develop evidence of disease by 2 years of age, with sensorineural hearing deficits (5–10 % of cases) and subsequent learning disabilities being the most important long-term sequelae.

Diagnosis. The most definitive method of diagnosis of CMV infection is by isolation of the virus from the blood, urine, or cervix. Several years ago, virus was often not detectable in culture for 2–6 weeks, but with newer techniques the virus is now detectable usually within days. A number of serologic studies are available for the detection of antibody to CMV, including indirect hemagglutination assay, ELISA, immunofluorescent assay, neutralization tests, and complement fixation (CF). CF assays are often inaccurate because of a high false-positive rate due to crossreactivity with other herpesviruses. CMV-specific IgM antibody tests are helpful but of limited value because 30 % of women with primary infections are initially seronegative, and the test result is positive in 10 % of women with recurrent infections. Acute and convalescent paired specimens demonstrating a significant increase in titer are suggestive of a primary infection. When maternal primary infection is suspected, or there are findings on ultrasonography that are suspicious of congenital CMV infection, prenatal diagnosis can be carried out by amniocentesis or fetal blood sampling. Ideally, prenatal diagnosis should occur beyond 21 weeks' gestation, as this optimizes the sensitivity of diagnostic tests. PCR and/or viral culture of amniotic fluid can be performed to detect CMV. PCR, including nested PCR, has been shown to have a sensitivity of 77–100 %, specificity of 67–99 %, PPV of 100 % and NPV of 93 %. Viral isolation has a sensitivity ranging from 50% to 72%, and a specificity of 97–100 %. PCR of amniotic fluid, when combined with viral isolation, has been shown to have a sensitivity of 84 % and a specificity of 100 %. Fetal blood can be tested for the presence of fetal IgM after 20 weeks' gestation, and has a sensitivity of 51–58 % and a specificity of 100 %. The presence of cord blood CMV-specific IgM, which is detectable in 60 % of infants with congenital infection, establishes the diagnosis. It is possible to obtain false-negative IgM titers when cordocentesis is performed early in the course of fetal infection; IgM levels correlate positively with abnormal fetal ultrasound findings and hematologic test results. PCR analysis of fetal blood for the presence of CMV DNA has a sensitivity of 41 %, whereas viral culture is only 7 % sensitive. Additional tests include searching for the presence of viremia (infectious CMV in leukocytes; sensitivity of 0–55 %), antigenemia (pp65-positive leukocytes; sensitivity 16–64 %), and messenger RNA (sensitivity 82 %). On the whole, fetal blood sampling and amniotic fluid analysis has sensitivity, specificity, PPV and NPV of 80 %, 99 %, 98 %, and 93 % respectively. As fetal blood sampling adds little additional value to amniotic fluid sampling, it should now be considered only for possible confirmatory testing of the fetus.

Management. No treatment other than symptomatic therapy is necessary for the immunocompetent adult with CMV infection. A variety of therapeutic agents — ganciclovir, adenosine arabinoside, acyclovir, idoxuridine, cytosine arabinoside, 5-fluoro-2′-deoxyuridine, leukocyte interferon, and transfer factor — have been administered for the treatment of congenital CMV infection, but none

has been found to be satisfactory because of toxicity or recurrence of infection after drug administration is terminated. Currently, there is no role for antenatal treatment of fetal CMV infection. Routine antepartum serologic screening for CMV is not recommended at this time. The detection of maternal CMV antibody before conception indicates prior infection, but the degree of protection that this immunity provides against congenital infection in subsequent pregnancies is unclear. The implications of a single antibody titer obtained during pregnancy are difficult to interpret. Even in a high-risk environment, the extent of risk for a seronegative pregnant woman by exposure is uncertain. One effective prevention strategy is the use of good handwashing, especially in high-risk settings such as daycare facilities or neonatal intensive care units.

Prevention. Vaccines have been investigated. As the vast majority of congenital CMV infections occur in instances of maternal primary infection, a reasonable strategy is to vaccinate seronegative women prior to conception. Vaccine development has included investigations into live-attenuated vaccines, recombinant virus vaccines, subunit vaccines, DNA vaccines, and peptide vaccines. None has been established as a superior method, and none has been adopted for routine use in humans. By the time pregnancy occurs, about 75 % of women will be immune to CMV. Of women who acquire CMV in pregnancy, some 5 % have a seriously damaged infant. Unlike rubella, there is no vaccination against the disease. If the disease is suspected, it can be confirmed by looking for the IgM specific to CMV. Transplacental passage is not inevitable and the organism may be sought in the fetus by means of chorionic villus sample (early) or fetal blood sample (late).

2.4. HUMAN IMMUNODEFICIENCY VIRUS INFECTION (HIV)

Etiology/Pathogenesis. Human immunodeficiency virus causes an incurable infection that leads ultimately to a terminal disease called acquired immunodeficiency syndrome (AIDS). Worldwide 25-30% of infected patients are women and 90% of them are 20-49 years of age. Incidence is difficult to work out but the fact remains that the disease is alarmingly increasing both in the developed and in developing countries. It is now a global problem. The prevalence even in low-risk population in America is close to 1 in 1000. The seropositivity rate among US pregnant women is 1–2 per 1000. In most Asian countries the infection rate is less than 0.5 %.

HIV viruses (HIV 1 and HIV 2) are RNA retroviruses having the enzyme reverse transcriptase, which permits genomic RNA to be transcribed into double stranded DNA. The virus attaches to T lymphocytes known as CD4+ cells whose action in the immune system is to combact viruses, bacteria and certain malignancies. Once the virus is into the genome of the host, it produces multiple copies of itself, which will eventually cause host cell damage. There is gradual

depletion of CD4+ cells. There is also failure of B lymphocytes to produce antibodies to HIV. These events lead to progressive loss of host immune defence and development of AIDS. Primary infection → 3–6 weeks → Acute syndrome (1 week – 3 months) → Immune response to HIV (1–2 weeks) → Clinical latency — about 10 years → AIDS. The main modes of transmission of HIV are — (1) Sexual contact (homosexual or heterosexual) (2) transplacental (3) exposure to infected blood or tissue fluids and (4) through breast milk.

Immunopathogenesis: Profound cell mediated immunodeficiency is the basic pathology as the HIV leads to slow but progressive destruction of T cells. The incubation period is about 1–3 weeks. After a peak viral load, there is gradual fall until a steady state of virus concentration is reached. This is known as set point which is a state of balance between the virus's ability to replicate and the host's ability to protect itself by neutralization and removal of virus. When the set point viral load is high → more destruction of host CD4 cells → progressive immunosuppression → opportunistic infections and cancers. The virus is present in blood and all body fluids and is transmitted by sexual contact (70 %), by parenteral exposure to infected blood or body fluids, or by transplacental passage of the virus from mother to fetus. The highest-risk groups for HIV infection are homosexuals, bisexual men, intravenous drug abusers, and hemophiliacs receiving blood transfusions. Others at high risk are prostitutes and heterosexual partners of men in the high-risk groups. All blood must be screened for HIV before transfusion to minimize transfusion risk. Women acquire the virus more easily from men rather than the reverse because the concentration of HIV in semen is high and mucosal breaks at the introitus or vagina with intercourse occur more commonly than do breaks in penile skin. Although anti-HIV antibodies develop within 12 weeks of exposure, 45–90 % of persons infected with HIV will develop symptoms of an acute infection similar to mononucleosis within a few months. They experience weight loss, fever, night sweats, pharyngitis, lymphadenopathy, and an erythematous maculopapular rash. Most of these symptoms resolve within a few weeks, although the patients remain infectious despite being asymptomatic. Some will progress to develop symptoms of AIDS-related complex (ARC), with early immunosuppression (decreased CD4+lymphocytes). ARC is usually marked by generalized lymphadenopathy, weight loss, diarrhea, malabsorption, and wasting. Some patients experience further immunosuppression and develop AIDS (any of the symptoms of acute sepsis, opportunistic infections, Kaposi's sarcoma, cognitive difficulties, or depression). Once AIDS has been diagnosed, mortality is 90 %. Immunologic abnormalities associated with AIDS include (but are not limited to) lymphopenia, decreased T-helper cells, decreased T-lymphocytes, hypergammaglobulinemia, and an inverted T4/T8 ratio.

Clinical manifistation. Initial presentation of an infected patient may be fever, malaise, headache, sore throat, lymphadenopathy and maculopapular rash. Primary illness may be followed by an asymptomatic period. Progression of the

disease may lead to multiple opportunistic infections with candida, tuberculosis, pneumocystis and others. Patient may present with neoplasms such as cervical carcinoma, lymphomas (Hodgkin's and non-Hodgkin's) and Kaposi's sarcoma. There may be associated constitutional symptoms like weight loss, lymphadenopathy or protracted diarrhea. CD4+ count < 200 cells/mm^3 is diagnostic of AIDS. The median time from infection to AIDS is about 10 years.

Maternal complications. Pregnancy per se has got no effect on the disease progression in HIV positive women. Increased incidence of abortion, prematurity, IUGR and perinatal mortality in HIV seropositive mothers still remains inconclusive. Maternal mortality and morbidity are not increased by pregnancy.

Fetal/neonatal complications. Vertical transmission to the neonates is about 14–25 %. Transmission of HIV 2 is less frequent (1–4 %) than for HIV 1 (15–40 %). Transplacental transmission occurs: 20 % before 36 weeks, 50 % before delivery and 30 % during labor. Vertical transmission is more in cases with preterm birth and with prolonged membrane rupture. Risks of vertical transmission is directly related to maternal viral load (measured by HIV RNA) and inversely to maternal immune status (CD4+ count). Maternal anti-retroviral therapy reduces the risk of vertical transmission by 70 % (see below). Breastfeeding increases transmission by 30–40 %. Male to female transmission is about double compared to female to male transmission. Rectal intercourse is more dangerous than vaginal. Parenteral transmission is the most potent route.

Diagnosis. The enzyme immunoassay (EIA) is used as a screening test for HIV antibodies. It is extremely sensitive (99.5 %), inexpensive but less specific. EIA kits are commercially available. Polymerase chain reaction (PCR) technique of amplifying viral DNA is also done for early diagnosis. This is then confirmed by Western blot test or immunofluorescence assay (IFA). The western blot detects specific viral antigens P24 (Capsid), GP41 (envelope) and GP 120/160 (envelope). False positive rate of Western blot is less than 1 in 10,000The human immunodeficiency virus (HIV) was first reported to cause disease in 1981. In the United States, AIDS is now the fiftleading cause of death among women of childbearing age. Moreover, it is the leading cause of death in this age group in New York City. This is now a worldwide crisis, with millions affected, especially in developing countries. One of the problems in recognition of HIV infection is a long, asymptomatic latency of 2 months to 5 years. The mean age at diagnosis of HIV infection is 35 years.

All pregnant women should be tested for human immunodeficiency virus (HIV) infection during the first prenatal visit. A second test during the third trimester, preferably at < 36 weeks' gestation, should be considered for all pregnant women and is recommended for those known to be at high risk for acquiring HIV, those who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women, and women seen in clinical settings in which prenatal screening identifies at least one pregnant women with HIV infection per 1,000

women screened. Diagnostic algorithms for HIV infection in pregnant women are not different than those for non-pregnant women. Pregnant women should be informed about being tested for HIV as part of the panel of prenatal tests; for women who decline, providers should address concerns that pose obstacles to testing and encourage testing at subsequent prenatal visits. Women who decline testing because they have had a previous negative HIV test result should be informed about the importance of retesting during each pregnancy. Women with no prenatal care should be tested for HIV at the time of delivery.

Testing pregnant women is important not only because knowledge of infection status can help maintain the health of the woman, but because it enables receipt of interventions (antiretroviral and obstetrical) that can substantially reduce the risk for perinatal transmission of HIV. After a pregnant woman has been identified as having HIV infection, she should be educated about the benefits of antiretroviral treatment for her health and for reducing the risk for transmission to her infant. In the absence of antiretroviral treatment, a mother's risk of transmitting HIV to her neonate is approximately 30% but can be reduced to < 2 % through antiretroviral treatment, obstetrical interventions (elective cesarean section at 38 weeks of pregnancy), and breastfeeding avoidance. Pregnant women who have HIV infection should be linked to an HIV care provider and given appropriate antenatal and postpartum treatment and advice. HIV antibody testing begins with the enzyme-linked immunosorbent assay (ELISA), which has a 95 % sensitivity and a 99 % specificity if repeatedly positive. If the ELISA is positive, a Western blot assay must be performed to confirm the diagnosis. False-negative results are rare unless the patient is too early in the disease to have formed antibodies. HIV screening (after informed consent has been obtained and assurances of confidentiality provided) should be encouraged for women in the following categories: intravenous drug users, prostitutes, sex partner(s) of men who are HIV positive or at risk for HIV, those with other sexually transmitted disease, those who received blood transfusions between 1978 and 1985, those with clinical signs and symptoms of HIV infection, inhabitants of a country with high endemic heterosexual HIV infection, prison inmates, and one who considers herself at risk.

Obstetrics management. Pregnancy does not appear to alter the progression of HIV infection, but the chance of the fetus acquiring the virus is 20–50 %. The neonate may be infected during labor and delivery by maternal blood or body fluids or may be infected during breastfeeding. The mode of delivery does not influence the development of pediatric AIDS. The acute illness associated with HIV in pregnancy may be misdiagnosed if HIV serologic testing is not performed. When HIV infection is diagnosed during pregnancy, treatment should be delayed because of the teratogenic potential of the medications used. The pregnant HIV-infected woman should be screened for other STDs, along with evaluation for opportunistic infection. A baseline serologic study for CMV and

toxoplasmosis, TB skin testing, and chest radiograph are recommended. Recently AZT and other chemotherapeutic agents have been found to decrease maternal-fetal and neonatal transmission of HIV. When caring for HIV positive mothers, health care providers should obtain the very latest information in this important and rapidly evolving area.

Care of the HIV-positive woman and her infant in the peripartum and postpartum interval includes protection of health care workers by using universal infection control guidelines (water-repellent gowns, gloves, masks, goggles for potential splash situations, wall or bulb suctioning). Scalp electrodes and fetal scalp blood samples should be avoided (potential entry site for HIV if fetus is not already infected). Circumcision should not be done if the neonate is HIV positive. Because anti-HIV IgG antibody passes through the placenta, the infant may be seropositive without being infected. Abnormal facial features have been described in some HIV-positive newborns, but this is not common. If neonatal/pediatric AIDS develops, the course of the disease is much more rapid than in adults, with death in months rather than years.

Prevention. Because there is no cure for HIV, current therapy only slows the progression of the disease. Hence, there is every reason to stress prevention. Other than abstinence or having a monogamous relationship with a known noninfected partner, using latex condoms lubricated with nonoxynol 9 is the most effective method of limiting the risk of infection. If a woman is HIV positive, she should be counseled, not to donate blood, plasma, tissue, or organs; to avoid pregnancy; to maintain a monogamous relationship; and to assiduously use condoms lubricated with nonoxynol 9 during any sexual contact.

2.5. HUMAN PAPILLOMAVIRUS INFECTION (HPV)

Etiology/Pathogenesis. Approximately 100 types HPV have been identified, at least 40 of which can infect the genital area. Most HPV infections are self-limited and are asymptomatic or unrecognized. Most sexually active persons become infected with HPV at least once in their lifetime. Oncogenic, high-risk HPV infection (HPV types 16 and 18) causes most cervical, penile, vulvar, vaginal, anal, and oropharyngeal cancers and precancers, whereas nononcogenic, low-risk HPV infection (HPV types 6 and 11) causes genital warts and recurrent respiratory papillomatosis. Persistent oncogenic HPV infection is the strongest risk factor for development of HPV-associated precancers and cancers. Of anogenital warts, 90 % are caused by nononcogenic HPV types 6 or 11; these types can be commonly identified before or at the same time anogenital warts are detected. HPV types 16, 18, 31, 33, and 35 are also occasionally found in anogenital warts (usually as co-infections with HPV 6 or 11) and can be associated with foci of high-grade squamous intraepithelial lesions (HSIL), particularly in persons who have HIV infection. In addition to anogenital warts, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

Clinical manifistation. Exophytic warts, also called condyloma acuminata, are typically caused by HPV types 6 and 11. They appear as friable, pink, fleshy skin appendages that vary greatly in size and are either broad based or pedunculated. Many lesions, however, are not visible to the naked eye. These flat endophytic condylomata are found with the use of colposcopy on the cervix, vagina, and vulva. Colposcopy uses a lighted, magnification system to view genital epithelium. A 3–5 % solution of acetic acid is applied to the area to be examined and allowed to absorb. Common colposcopic findings in HPV infection are irregularly defined patches that appear shiny and white and are not confined to the transformation zone. Any suspicious lesion should be biopsied.

Anogenital warts are usually asymptomatic, but depending on the size and anatomic location, they can be painful or pruritic. They are usually flat, papular, or pedunculated growths on the genital mucosa. Anogenital warts occur commonly at certain anatomic sites, including around the vaginal introitus, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Warts can also occur at multiple sites in the anogenital epithelium or within the anogenital tract (cervix, vagina, urethra, perineum, perianal skin, anus, and scrotum). Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse, but they also can occur in men and women who have not had a history of anal sexual contact.

Maternal complications. Having HPV does not make it harder for a woman to get pregnant or carry a pregnancy to term. However, some of the precancers or cancers that HPV can cause, and the treatments needed to treat them, might lower a woman's ability to get pregnant or have an uncomplicated delivery. Treatments are available for the conditions caused by HPV, but not for the virus itself. Warty lesions have a tendency to grow and become more vascularized during pregnancy. The only contraindications to a vaginal delivery are extensive lesions that might result in dystocia and lesions that might bleed heavily with birth trauma. Although some suggest removal of large warts during pregnancy, this practice is of uncertain benefit.

Anogenital warts can proliferate and become friable during pregnancy. Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete.

Fetal/neonatal complications. Vertical transmission of HPV is rare, but can result in respiratory papillomatosis in the exposed infant. The exact mode of spread is unknown.

Diagnosis. Given the fact that transmission rates are low, and adverse perinatal outcome unknown, it is not recommended that pregnant patients be routinely screened for HPV. Sexual partners of infected women should be examined for the presence of warts, and those infected should be schooled in safe sexual practices to avoid transmission to uninfected partners.

The majority of HPV lesions are subclinical, identified only with colposcopy, cytology, tissue examination, or in situ hybridization techniques. They

can be found on the vulva, vagina, cervix, and anorectal region. More recently, PCR technology has been utilized for the detection of HPV.

HPV tests are available to detect oncogenic types of HPV infection and are used in the context of cervical cancer screening and management or follow-up of abnormal cervical cytology or histology. These tests should not be used for male partners of women with HPV or women aged < 25 years, for diagnosis of genital warts, or as a general STD test.

The application of 3–5 % acetic acid, which might cause affected areas to turn white, has been used by some providers to detect genital mucosa infected with HPV. The routine use of this procedure to detect mucosal changes attributed to HPV infection is not recommended because the results do not influence clinical management.

The diagnosis of condyloma acuminata is usually made on clinical grounds. Given the high prevalence of subclinical disease, cytology, tissue biopsy, and in situ hybridization techniques are often necessary to make the diagnosis. In the least sensitive of laboratory methods available, cytologic evidence in the form of koilocytosis has been found in approximately 2 % of women receiving Pap smears. Cervical biopsies tested for both koilocytosis and HPV antigen found that 20 % were positive by both methods. The most sensitive detection method for HPV has been DNA in situ hybridization. One study tested routine Pap smears using this technique and found that 16 % had evidence of HPV types 6, 11, 16, or 18.

Diagnosis of anogenital warts is usually made by visual inspection. The diagnosis of anogenital warts can be confirmed by biopsy, which is indicated if lesions are atypical (pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated lesions). Biopsy might also be indicated in the following circumstances, particularly if the patient is immunocompromised (including those infected with HIV):

1) the diagnosis is uncertain;

2) the lesions do not respond to standard therapy;

3) the disease worsens during therapy.

HPV testing is not recommended for anogenital wart diagnosis, because test results are not confirmatory and do not guide genital wart management

Management. Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. Precancerous lesions are detected through cervical cancer screening (see Cervical Cancer, Screening Recommendations); HPV-related precancer should be managed based on existing guidance.

During pregnancy, the best approach to treatment is removal of lesions by excision, electrocautery, or cryosurgery. TCA application has been used in pregnancy without adverse effects. Laser therapy is another alternative among pregnant women with extensive disease. Podofilox (podophyllotoxin), podo-

phyllin, and sinecatechins should not be used during pregnancy. Imiquimod appears to pose low risk but should be avoided until more data are available.

The CDC suggests that the treatment modality should be changed if the patient has not improved substantially after three provider-administered treatments or if warts have not completely cleared following six treatments. The use of podophyllin, podofilox, and imiquimod are contraindicated in pregnancy.

Obstetrics management. Cesarean section is not recommended in the presence of genital warts in order to prevent vertical transmission of HPV. Rarely, HPV types 6 and 11 can cause respiratory papillomatosis in infants and children, although the route of transmission (transplacental, perinatal, or postnatal) is not completely understood. Whether cesarean section prevents respiratory papillomatosis in infants and children also is unclear; therefore, cesarean delivery should not be performed solely to prevent transmission of HPV infection to the newborn. Cesarean delivery is indicated for women with anogenital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding. Pregnant women with anogenital warts should be counseled concerning the low risk for warts on the larynx of their infants or children (recurrent respiratory papillomatosis).

Prevention. Two HPV vaccines can prevent diseases and cancers caused by HPV. The Cervarix and Gardasil vaccines protect against most cases of cervical cancer; Gardasil also protects against most genital warts. HPV vaccines are recommended routinely for boys and girls aged 11–12 years; either vaccine is recommended for girls/women, whereas only one vaccine is recommended for boys/men. These vaccines are safe and effective.

Condoms used consistently and correctly can lower the chances of acquiring and transmitting HPV and developing HPV-related diseases (genital warts and cervical cancer). However, because HPV can infect areas not covered by a condom, condoms might not fully protect against HPV. Limiting number of sex partners can reduce the risk for HPV. However, even persons with only one lifetime sex partner can get HPV. Abstaining from sexual activity is the most reliable method for preventing genital HPV infection.

2.6. RUBELLA

Etiology/Pathogenesis. Rubella, or German measles, is caused by a single-stranded RNA virus that is a member of the togaviridae. There are two major genotypes, with European, North American, and Japanese isolates differing from some found in India and China. Given the stability of the viral genome, and the protective effect of IgG antibody, the humoral-mediated response confers immunity against future reinfection. The success of vaccination against rubella, and the subsequent decline of congenital rubella infection (CRI), stands as one of the major achievements of twentieth-century perinatal and neonatal medicine After the initial decrease in the incidence of congenital rubella syndrome (CRS),

the incidence has plateaued at approximately 0.05 cases per 100000 live births for the past 10 years because of continued rubella infection in women of childbearing age. Similar to the distribution of rubella infection in adults, during 1997–1999 in the United States, 81 % of infants reported to have CRI were Hispanic, with 92 % of their mothers having been foreign born (CDC, unpublished data, 2000).

Rubella virus is spread by respiratory droplets. This requires prolonged, close exposure. The virus is present in the nasopharynx and spreads via the lymphatics and then blood. It is less communicable than varicella, with an 80% attack rate. Fetal infection requires maternal viremia and placental transmission. Viremia has been thought to occur only with primary infection. Rare cases of reinfection leading to CRS have been reported. Serologic evidence of fetal exposure to rubella has been documented after inadvertent vaccination in pregnancy. To date, no cases of congenital defects secondary to CRS have been reported due to vaccine. Nevertheless, vaccine administration is contraindicated in pregnancy because the theoretical risk of CRS after vaccination, although low, may not be zero. Virus is shed in breast milk as well.

Clinical manifistation. Rubella is transmitted by respiratory droplet exposure. Maternal Rubella infection is manifested by rash, malaise, fever, lymphadenopathy and polyarthritis. Fetal infection is by transplacental route throughout pregnancy. Risk of major anomalies when this infection occurs in first, second and third month is approximately 50 %, 25 % and 10 % respectively. Multisystem abnormalities are seen following congenital rubella infection. Congenital rubella syndrome (CRS) predominantly include cochlear (sensorineural deafness), cardiac (septal defects, PDA), hematologic (anemia, thrombocytopenia), liver and spleen (enlargement, jaundice), ophthalmic (cataracts, retinopathy, cloudy cornea), bone (osteopathy) and chromosomal abnormalities. The virus predominantly affects the fetus and is extremely teratogenic if contracted within the first trimester. There is increased chance of abortion, stillbirth and congenitally malformed baby. Infants born with congenital rubella shed the virus for many months and is a source of infection to others.

Fetal/neonatal complications. The rubella virus is extremely teratogenic. Many infants are abnormal and maldeveloped if the mother contracts rubella during the first trimester of pregnancy. Excluding patients affected during epidemics, the risk of congenital anomalies occurring during the first 3 months of pregnancy declines from almost 50 % (first month) to about 10 %. After the first trimester, the danger of anomalies is negligible, but vision or hearing defects or both are common. Fetal defects include cataracts, congenital heart disease, dental dysplasia, deafness, and mental retardation. It may take 1–2 years to be certain of the extent of infant defects. There is some evidence that an abnormal child may be born of a mother who has previously been vaccinated but contracts a subclinical form of the disease when reexposed during pregnancy.

Neonatal exposure to rubella during breastfeeding has not been associated with morbidity. Prolonged viral shedding from the CRS infant may be a source of infection. Virus has been isolated in the urine, cerebrospinal fluid, and even the lens of CRS patients. The variable risk of CRS at different gestational ages has long been recognized. Rubella infection before implantation has been implicated in spontaneous abortion, stillbirth, neonatal death, and CRS. Enders and co-workers reported that rubella occurring from 12 days to 12 weeks after the last menstrual period (LMP) resulted in an 81–90 % fetal infection rate. No infection was noted if the rash appeared before the LMP or up to 11 days after the LMP. Cradock-Watson and Ridehalgh reviewed rates of rubella infection after the first trimester. The overall rate of CRI (seropositivity, with or without clinical disease) was 29 % based on rubella-specific IgM and 49 % based on persistence of rubella-specific IgG after 8 months of age. Gestational age-specific rates of CRI ranged from 12 % when infection occurred at 24–28 weeks to 58 % at 36–40 weeks.

The pathogenesis of congenital defects includes impairment in organogenesis due to decreased mitosis and damage secondary to scarring and persistent infection. Abnormalities resulting from impaired organogenesis occur with maternal infection in the first trimester. Other abnormalities, such as progressive hearing loss and pulmonic or aortic stenosis, are due to ongoing damage caused by persistent infection and immune response. In addition, first-trimester rubella infection is believed to cause abortion. Current surveillance practices do not provide information on the incidence of pregnancy loss.

Congenital infection may be divided into three categories based on its manifestations: CRS, extended CRS, and delayed CRS. Newborn rubella, or CRS, and extended CRS are apparent at birth. Delayed manifestations of congenital infection may not be apparent for years or decades. Four major defects in CRS, in order of decreasing frequency, are deafness, mental retardation, heart lesions, and ophthalmologic abnormalities. Types of malformation are gestational-age specific. Cataracts and cardiac lesions are present when infection occurs before 8 weeks. Deafness occurs with infection before 16 weeks, and retinopathy with infection before 130 days. Timing of fetal exposure is at best estimated because of difficulties in dating gestational age and lack of information regarding the incubation period of fetal rubella infection. Sever and associates in the Collaborative Perinatal Research Study (CPRS) of 1964, reported that deafness was the most common single defect and was present in 100 % of infants with multiple defects resulting from first-trimester infection. Conversely, eye defects, with cataracts and glaucoma being most frequent, were present only with other abnormalities. Cardiac lesions include ventricular septal defect, patent ductus arteriosus, and peripheral pulmonic stenosis. Thrombocytopenic purpura (blueberry muffin rash), hepatosplenomegaly, osseous lesions, meningoencephalitis, and rubelliform rash may also be present in CRS. Contrary to the previously held perception that second-

and third-trimester rubella infections are without clinical consequence in the fetus, abnormalities (including developmental delay, hearing loss, growth retardation, pulmonic stenosis, and thrombocytopenia) have been found in 15 out of 24 infants exposed to rubella at between 14 and 31 weeks' gestation. The spectrum of extended CRS includes cerebral palsy, mental retardation, developmental and language delay, seizures, cirrhosis, growth retardation, and immunologic disorders (hypogammaglobulinemia). Delayed manifestations of CRI include endocrinopathies, late-onset deafness and ocular damage, renovascular hypertension, and encephalitis. Long-term follow-up of CRS patients revealed a 20 % incidence of diabetes mellitus by the age of 35 years. Other endocrinopathies include thyroid dysfunction and growth hormone deficiency. Deafness and ocular and vascular damage may be due to ongoing infection with scarring and inflammation. Delayed manifestations of CRS are thought to be due to circulating immune complexes. Delayed manifestations occur in more than 20% of those with initially symptomatic CRS. The incidence of delayed defects in those with asymptomatic CRI and their gestational age-related risk are not clear. Data from the CPRS showed delayed effects in almost two-thirds of those infected in the third trimester. Although major malformations due to infection in the first trimester may be devastating, the adverse effects from later infection are clearly not minor. Progressive panencephalitis has been likened to subacute sclerosing panencephalitis due to rubeola infection and is a different entity from the encephalitis present at birth. Hypogammaglobulinemia may be a delayed result of CRI; altered cell-mediated immunity is necessary for continued latent viral infection. Because of altered cell-mediated immunity, the rubella virus persists in the congenitally infected person for up to a year, and perhaps longer.

Postnatally acquired rubella is a mild or asymptomatic infection. The incubation period is 14–21 days, with viral shedding beginning 1 week before the onset of rash. The rash is macular and lasts 3 days, hence the name 3-day measles. Malaise, fever, and postauricular and suboccipital adenopathy are also common. Arthralgias are common in adult women; arthritis, neuritis, encephalitis, and thrombocytopenia are rare in postnatal infection. Because these symptoms are nonspecific, diagnosis should be made on serologic rather than clinical grounds.

Diagnosis. Test for rubella specific antibody (IgM) should be done within 10 days of the exposure to know whether the patient is immune or not. Rubella specific IgG antibodies are present for life after natural infection or vaccination. If the patient is not immune, question of therapeutic termination should be seriously considered. Detection of viral RNA by PCR is possible. Prenatal diagnosis of rubella virus infection using PCR can be done from chorionic villi, fetal blood and amniotic fluid samples.

Clinical diagnosis of postnatal infection is unreliable and must be confirmed by serology. Before the availability of serologic tests of rubella infection and immunity, virus isolation was attempted. The rubella virus is difficult to isolate. Serologic evidence of maternal primary infection includes the presence

of rubella-specific IgM, which can persist for 8–12 weeks following acute infection. In the past, the presence of a fourfold increase in hemagglutination inhibition titer on acute and convalescent sera also provided evidence of a primary infection; commercially available enzyme immunoassays for rubella IgM and IgG are now routinely performed by most laboratories. Indirect antibody assays are more prone to false-positive IgM results, due in part to crossreactivity with other IgM antibodies or with rheumatoid factor; hence, a second confirmatory test for rubella IgM by a different modality should be performed, especially before 20 weeks' gestation. Prenatal diagnosis of CRI is possible. The presence of rubella-specific IgM in fetal blood confirms infection. Fetal immunocompetence is attained in the mid-second trimester; therefore, to avoid a false-negative result, fetal blood sampling to detect IgM must be delayed until 20–22 weeks' gestation. First-trimester confirmation of fetal infection was described by Terry and colleagues by detecting virus-specific antigen and RNA in a chorionic villus sample. This method is superior to virus isolation in the products of conception. Nevertheless, the presence of rubella virus in the placenta may not correlate with fetal infection. More recently, the development of PCR technology has the potential of rendering fetal blood sampling virtually unnecessary. With reverse transcriptase PCR (RT PCR), amniotic fluid obtained via amniocentesis (when performed at least 8 weeks after acute maternal infection or at 15 weeks of gestation) can be evaluated for virus-specific RNA; this has a sensitivity of 87–100 %. However, cases have been reported of finding rubella RNA and IgM in fetal blood following negative PCR analysis of amniotic fluid at 19 and 23 weeks.

Management. Prevention. Prevention of in utero rubella infection requires the acquisition of immunity by all persons before the childbearing years. Programs to ensure vaccination of all schoolchildren, susceptible college students, and military personnel help, but do not eradicate CRI. Missed opportunities for vaccination of adults still occur and contribute to the continued existence of CRS. Congenitally infected neonates are also a source of virus. The rubella vaccine is a live-attenuated virus that yields immune responses similar to native infection; the rate of seroconversion is as high as 95 % in individuals older than 11 months of age. Long-term efficacy exceeds 90 %, but antibody titers can decline over time. As mentioned previously, administration of the vaccine is contraindicated in pregnancy as there is a theoretical risk of acquiring CRS, although there have never been such cases documented worldwide. There is no specific antiviral therapy for rubella infection. If in utero exposure to rubella virus is documented, the woman should be counseled as to the risks and consequences of CRI. Prenatal diagnosis, even in the first trimester, is possible. With the potentially devastating effects of first-trimester infection, a patient may choose to terminate the affected pregnancy if the diagnosis is made in a timely manner. Thus, rubella screening titers (specific serum hemagglutinating antibody) are considered routine in antenatal care to demonstrate the susceptibility to rubella.

Prophylactic immune serum globulin may prevent the rash but not the viremia of rubella, even when given before exposure to the disease. Therefore, the virus remains a significant threat to the fetus. This has led to the recommendation that immune serum globulin is rarely indicated in pregnancy. Attenuated rubella virus vaccine will confer active immunity for a prolonged but uncertain period. Because the vaccine can potentially infect the fetus, it is recommended that immunization should be carried out in women only if they are not pregnant and pregnancy can be avoided for 3 months after vaccination. Although this remains a good guideline, when vaccination has occurred during pregnancy, there have been few, if any, demonstrable teratic effects. Reactions to the vaccine may include mild fever, local soreness at the site of injection, and arthralgia. Spread of the virus to others is not a problem.

Active immunity can be conferred in non-immune subjects by giving live attenuated rubella virus vaccine preferably during 11–13 years. It is not recommended in pregnant women. When given during the child-bearing period, pregnancy should be prevented within three months by contraceptive measure. However, if pregnancy occurs during the period, termination of pregnancy is not recommended.

2.7. INFLUENZA

Etiology/Pathogenesis. Influenza viruses belong to the myxovirus group and cause the clinical entity of influenza that occurs in epidemics. Type A influenza is responsible for most epidemics and is associated with more severe disease, whereas types B and C occur less frequently.

The frequency and severity of influenza outbreaks have been related to changes in the viral antigens. The major antigenic changes occur at 10- to 30-year intervals and are associated with severe infection because of the absence of protective anti-bodies. Two major pandemics occurred in 1918 and in 1957–1958. More than 20 million deaths occurred worldwide during the pandemic of 1918.111.

Clinical manifistation. With a short incubation period of 1-4 days, influenza presents with abrupt onset of an upper respiratory infection, fever, malaise, myalgia, and headache. With wide clinical variability, the major portion of the disease lasts approximately 3 days in most cases.

Definitive diagnosis can be made by isolation of the virus from throat washings during acute illness or by serologic confirmation of a fourfold rise in antibody. Although these antibodies are of the CF or hemagglutination inhibition types, they are rarely indicated clinically.

Influenza virus causes acute upper respiratory tract illness, characterized by the abrupt onset of fever, chills, headache, myalgias, malaise, a dry cough, and nasal discharge. GI manifestations and conjunctivitis can also be present.

The incubation period ranges from 1 to 5 days. Most cases of influenza are self-limited. Complications include pneumonia, occurring in up to 12 % of influenza-infected pregnant women, Reye's syndrome, and disseminated intravascular coagulation (DIC). Changes in the immune, cardiac and respiratory systems likely increase the risk of severe illness in pregnant women infected with influenza.

Maternal complications. For the obstetrician, the major concern of influenza infection in pregnancy is the increased likelihood of potentially life-threatening pneumonia. From reports from the epidemics of 1918 and 1957, it appears that pregnant women were disproportionately represented in individuals dying of influenza.

In addition, reported estimates of overall maternal mortality were approximately 27 %, with a mortality of up to 61 % in cases complicated by pneumonia prior to the era of treatment.112 It is not certain, however, whether pregnant women are more likely to develop influenza or whether they are more likely to develop influenza pneumonia. Yet, if influenza pneumonia develops in pregnancy, it is more severe. Deaths among pregnant women with influenza may result from secondary bacterial infection and from primary influenza pneumonia without secondary superinfection.

Fetal/neonatal complications. Contradictory data exist on the effects of influenza on abortion, prematurity, and congenital anomalies. These studies may be summarized as noting that the vast majority of women who have influenza in pregnancy have normal outcomes and that there seems to be little influence on congenital abnormalities, intrauterine growth, prematurity, or stillbirth.

Diagnosis. Rapid influenza diagnostic tests (RIDTs) are immunoassays identifying influenza A and B viral nucleoproteins in 15 minutes or less. RIDTs are very speci ⌈c (90–95 %); however, sensitivity is limited (10–70 %), with the potential for false-negative results during periods of high influenza incidence. False-positive results occur when influenza is at low prevalence. Some RIDTs distinguish between influenza A and B, but they cannot determine viral subtype.

The optimal time of specimen collection is within 48 to 72 hours of illness onset.31 Confrmation is via RT-PCR, culture, ELISA, or immunofluorescence of respiratory secretions; immunofluorescence and RT-PCR have the most rapid turnaround.

Management. Osteltamivir Influenza A and B NA inhibitor Treatment 75 mg BID 5 days None Prophylaxis 75 mg daily 7–10 days; Zanamivir Influenza A and B NA inhibitor Treatment 10 mg BID inhaled 5 days Underlying respiratory disease prophylaxis 10 mg daily, inhaled 7–10 days Chemoprophylaxis can be given to high risk, unvaccinated women exposed within 48 hours of presentation; alternative therapy for infection includes amantadine or rimantidine, which block M2 channel activity in influenza A. However, there is significant viral resistance to these drugs.

Obstetrics management. Pregnant women suspected to be infected with influenza should be treated immediately, without delay for diagnostic conformation. The recommended treatment for both seasonal and pandemic influenza infection is osteltamivir (dosages are shown in Table 50–5); acetaminophen should be used as an antipyretic and additional recommendations regarding adjunctive therapy are presented in Chapter 37. The preterm birth rate following pandemic H1N1 infection was 30 %, and increased preterm parturition also occurs following seasonal influenza infection; so appropriate monitoring should be undertaken, particularly in women with asthma, smoking, obesity, chronic hypertension, delayed treatment.

Prevention. ACOG and the CDC recommend vaccination of all pregnant women during influenza season (October-May) using the intramuscular, inactivated vaccine. The World Health Organization (WHO) and U.S. Public Health Service recommend the strains to be included in the annual vaccine based on recent prevalence; the vaccine is produced in eggs, which should be taken into account for patients with allergies. The optimal time to vaccinate patients is in October and November to minimize the risk of acquiring influenza; however, vaccination is safe and effective at any time of the year or gestational age. A study of 2000 pregnant women receiving the inactivated vaccine demonstrated no adverse fetal effects and safety in breastfeeding women; moreover, maternal vaccination also protects infants up to 6 months of age. The intranasal vaccine contains live virus and should not be used during pregnancy.

3. BACTERIAL INFECTIONS

3.1. CHLAMYDIAL INFECTION

Etiology/Pathogenesis. Chlamydia trachomatis is an obligate intracellular microorganism with a cell wall similar to that of gram-negative bacteria. Although they are classified as bacteria, contain both DNA and RNA, and divide by binary fission. Chlamydia grow only intracellularly, as do viruses. Since most of the C. trachomatis serotypes attack only columnar epithelial cells (except the aggressive L serotypes), signs and symptoms tend to be localized to the infected area (e.g., eye or genital tract) without deep tissue invasion.

Chlamydial infection is becoming the common sexually transmitted pathogen. The organisms are found in urethra, endocervix and rectum. C. trachomatis is an obligate intracellular bacteria. The adverse effects in pregnancy are: Preterm labor, PROM, Chorioamnionitis, stillbirth, perihepatitis (Fitz-Hugh-Curtis syndrome). Puerperal endometritis or acute salpingo-oophoritis may develop. Neonates may develop conjunctivitis or pneumonia.

C. trachomatis cervical and tubal infections occur in women of young age (2–3 times higher in women 20 years), with numerous sexual partners, of low socioeconomic status, with other STDs, and with oral contraceptive use. Barrier contraception tends to decrease the infection rate. Pregnant women have an incidence of 8–12 %.

Clinical manifistation. Typically, a mucopurulent discharge develops with cervical chlamydial infection, and the cervix shows hypertrophic inflammation (mucopurulent cervicitis). The primary complication of C. trachomatis cervical infection is salpingitis. Unfortunately, if the patient is pregnant and untreated, the vaginally delivered neonate will develop chlamydial conjunctivitis in 50 % of cases and late onset pneumonitis in 10 %. Premature delivery and early postpartum endometritis are also associated problems.

C. trachomatis salpingitis may be as prevalent as that caused by N. gonorrhoeae. However, there are marked differences in the pathophysiology and symptomatology. C. trachomatis salpingitis (which is also an ascending infection) has an insidious onset, it usually causes minimal symptoms, and the organism remains in the tube (primarily in the epithelium) for months. In contrast, N. gonorrhoeae infections have an acute onset, cause more acute symptoms, and remain in the tubes only 24–48 h. Gonorrheal infections appear to have a much greater cytotoxic effect on the tubal epithelium.

Although C. trachomatis salpingitis usually causes fewer symptoms, the gross appearance of the tubes suggests even more severe involvement. Salpingitis is a consequence of C. trachomatis cervicitis. Treatment of C. trachomatis salpingitis may be accomplished with tetracyclines or erythromycin. The sequelae of C. trachomatis salpingitis include ectopic pregnancy and infertility, although the exact incidence of these complications is unknown.

Maternal complications. Urethritis and bartholinitis are manifested by dysuria and purulent vaginal discharge. Chlamydial cervicitis spreads upwards to produce endometritis and salpingitis. Chlamydial salpingitis is asymptomatic in majority of the cases. It causes tubal scarring resulting in infertility and ectopic pregnancy. It is the more common cause of perihepatitis (Fitz-Hugh-Curtis syndrome) than gonococcus. The spread to the liver from the pelvic organs is via lymphatics and the peritoneal cavity.

Fetal/neonatal complications. Prenatal screening and treatment of pregnant women is the best method for preventing chlamydial infection among neonates. C. trachomatis infection of neonates results from perinatal exposure to the mother’s infected cervix.

Neonates born to mothers who have untreated chlamydia are at high risk for infection; however, prophylactic antibiotic treatment is not indicated, as the efficacy of such treatment is unknown. Infants should be monitored to ensure appropriate treatment if symptoms develop.

Although the efficacy of neonatal ocular prophylaxis with erythromycin ophthalmic ointments to prevent chlamydia ophthalmia is not clear, ocular

prophylaxis with these agents prevents gonococcal ophthalmia and therefore should be administered. Initial C. trachomatis neonatal infection involves the mucous membranes of the eye, oropharynx, urogenital tract, and rectum, although infection might be asymptomatic in these locations. Instead, C. trachomatis infection in neonates is most frequently recognized by conjunctivitis that develops 5–12 days after birth. C. trachomatis also can cause a subacute, afebrile pneumonia with onset at ages 1–3 months. Although C. trachomatis has been the most frequent identifiable infectious cause of ophthalmia neonatorum, neonatal chlamydial infections (including ophthalmia and pneumonia) have occurred less frequently since the institution of widespread prenatal screening and treatment of pregnant women.

Ophthalmia neonatorum caused by C. trachomatis. A chlamydial etiology should be considered for all infants aged ≤ 30 days that have conjunctivitis, especially if the mother has a history of chlamydia infection. These infants should receive evaluation and appropriate care and treatment.

Chlamydia pneumonia in infants typically occurs at 1–3 months and is a subacute pneumonia. Characteristic signs of chlamydial pneumonia in infants include 1) a repetitive staccato cough with tachypnea and 2) hyperinflation and bilateral diffuse infiltrates on a chest radiograph. In addition, peripheral eosinophilia (≥ 400 cells/mm^3) occurs frequently. Because clinical presentations differ, all infants aged 1–3 months suspected of having pneumonia (especially those whose mothers have a history of chlamydial infection) should be tested for C. trachomatis and treated if infected.

Follow-up of infants is recommended to determine whether the pneumonia has resolved, although some infants with chlamydial pneumonia continue to have abnormal pulmonary function tests later in childhood.

Diagnosis. Detection of C. trachomatis infection at repeat screening during the third semester is not uncommon in adolescent and young adult women, including in those without C. trachomatis detected at the time of initial prenatal screening. Women aged < 25 years and those at increased risk for chlamydia (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) should be rescreened during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant.

Diagnosis of C. trachomatis urethral infection in men can be made by testing a urethral swab or first-catch urine specimen. NAATs are the most sensitive tests for these specimens and therefore are recommended for detecting C. trachomatis infection. NAATs that are FDA-cleared for use with vaginal swab specimens can be collected by a provider or self-collected in a clinical setting. Self-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs, and women find this screening strategy highly acceptable.

Sensitive and specific methods used to diagnose chlamydial ophthalmia in the neonate include both tissue culture and nonculture tests (direct fluorescence antibody (DFA) tests and NAAT). DFA is the only nonculture FDA-cleared test for the detection of chlamydia from conjunctival swabs; NAATs are not FDA-cleared for the detection of chlamydia from conjunctival swabs, and clinical laboratories must verify the procedure according to CLIA regulations. Specimens for culture isolation and nonculture tests should be obtained from the everted eyelid using a dacron-tipped swab or the swab specified by the manufacturer's test kit; for culture and DFA, specimens must contain conjunctival cells, not exudate alone. Ocular specimens from neonates being evaluated for chlamydial conjunctivitis also should be tested for N. gonorrhoeae.

Management. Doxycycline is contraindicated in the second and third trimesters of pregnancy. Human data suggest ofloxacin and levofloxacin present a low risk to the fetus during pregnancy, with a potential for toxicity during breastfeeding; however, data from animal studies raise concerns about cartilage damage to neonates. Thus, alternative drugs should be used to treat chlamydia in pregnancy. Clinical experience and published studies suggest that azithromycin is safe and effective. Test-of-cure to document chlamydial eradication (preferably by NAAT) 3–4 weeks after completion of therapy is recommended because severe sequelae can occur in mothers and neonates if the infection persists. In addition, all pregnant women who have chlamydial infection diagnosed should be retested 3 months after treatment.

Treatment of ophthalmia neonatorum: Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days; alternative regimen — Azithromycin suspension, 20 mg/kg/day orally, 1 dose daily for 3 days. Partners mothers of infants who have ophthalmia caused by chlamydia and the sex partners of these women should be evaluated and presumptively treated for chlamydia.

Treatment of chlamydia pneumonia — Azithromycin 20 mg/kg/day orally, 1 dose daily for 3 days. Because the effectiveness of erythromycin in treating pneumonia caused by C. trachomatis is approximately 80%, a second course of therapy might be required. Data on the effectiveness of azithromycin in treating chlamydial pneumonia are limited.

3.2. MYCOPLASMA INFECTION

Etiology/Pathogenesis. M. genitalium was first identified in the early 1980s and has become recognized as a cause of male urethritis, responsible for approximately 15–20% of nongonococcal urethritis (NGU) cases, 20–25 % of nonchlamydial NGU, and approximately 30 % of persistent or recurrent urethritis. While M. genitalium is often the sole pathogen detected, coinfection with C. trachomatis is not uncommon in selected areas. The pathogenic role of M. genitalium is less definitive in women than it is in men. M. genitalium can be found

in the vagina, cervix, and endometrium and, like chlamydial and gonococcal infections, M. genitalium infections in women are commonly asymptomatic. M. genitalium can be detected in 10–30 % of women with clinical cervicitis, and most studies have found that this organism is more common among women with cervicitis than those without this syndrome.

Clinical manifistation. M. genitalium is found in the cervix and/or endometrium of women with PID more often than in women without PID, and endosalpingitis develops in nonhuman primates after inoculation with M. genitalium, suggesting that this organism can cause PID. M. genitalium has been detected in 2–22 % of PID cases (median: 10 %) depending on the setting, but the frequency with which M. genitalium-infected women experience PID has been under studied. Although one study in Sweden reported a substantial increase in risk for postabortal PID among women with M. genitalium, the proportion of M. genitalium-positive women who subsequently experienced PID in two other studies was relatively low (< 5 %), and evidence from serologic studies assessing the association of PID with antibody to M. genitalium is inconsistent. Overall, evidence suggests that M. genitalium can cause PID, but that this occurs less frequently than it does with C. trachomatis. A few seroepidemologic studies have found that women with tubal factor infertility are more likely to have antibodies to M. genitalium than fertile women, suggesting that this organism might cause female infertility.

Maternal complications. Fetal/neonatal complications. Mycoplasma hominis and Ureaplasma spp. have been associated with adverse pregnancy outcomes such as preterm labour and preterm premature rupture of membranes. However, as these bacteria can reside in the normal vaginal flora, there are controversies regarding their true role during pregnancy and so the need to treat these organisms. On the basis of certain reports, M. genitalium was uncommonly identified in women who experience adverse pregnancy outcomes, but was associated with increased risk for preterm delivery in one U.S. and another Peruvian study. Data are scarce regarding M. genitalium and ectopic pregnancy.

Diagnosis. M. genitalium is a slow-growing organism. Culture can take up to 6 months, and only a few laboratories in the world are able to recover clinical isolates. Therefore, NAAT is the preferred method for M. genitalium detection. In research settings, M. genitalium is diagnosed by NAAT testing of urine, urethral, vaginal, and cervical swabs and through endometrial biopsies, typically using in-house PCR or assays intended for research use only. NAAT tests (polymerase chain reaction or transcription mediated amplification) for M. genitalium are available in some large medical centers and commercial laboratories, but there is no diagnostic test for M. genitalium that is cleared by the FDA for use in the United States. In the absence of validated tests, M. genitalium should be suspected in cases of persistent or recurrent urethritis and may be considered in persistent or recurrent cases of cervicitis and PID.

Management. M. genitalium lacks a cell wall, and thus antibiotics targeting cell-wall biosynthesis (beta-lactams including penicillins and cephalosporins) are ineffective against this organism. Given the diagnostic challenges, treatment of most M. genitalium infections will occur in the context of syndromic management for urethritis, cervicitis, and PID.

Urethritis and cervicitis (for non-pregnant). The 7-day doxycycline regimen recommended for treatment of urethritis is largely ineffective against M. genitalium with a median cure rate of approximately 31 %. The 1-g single dose of azithromycin was significantly more effective against M. genitalium than doxycycline in two randomized urethritis treatment trials and is preferred over doxycycline. Persons with treatment failures after the 1-g azithromycin regimen frequently have macrolide-resistant strains, suggesting that single-dose azithromycin therapy might select for resistance. A longer course of azithromycin (an initial 500-mg dose followed by 250 mg daily for 4 days) might be marginally superior to the single dose regimen. However, in some settings, approximately 50 % of all M. genitalium infections are caused by organisms that are already resistant to azithromycin, and persons who do not respond to the 1-g azithromycin regimen generally do not benefit from retreatment with the extended dose regimen. Moxifloxacin (400 mg daily for 7, 10 or 14 days) has been successfully used to treat M. genitalium in men and women with previous treatment failures, with cure rates of 100% in initial reports. However, moxifloxacin has been used in only a few cases, and the drug has not been tested in clinical trials. Although generally considered effective, studies in Japan, Australia, and the United States have reported moxifloxacin treatment failures after the 7 day regimen.

Microbiological screening of M. hominis and pre-emptive antibiotic therapy of symptomatic pregnant women in late pregnancy might represent a beneficial strategy to reduce premature labour and neonatal complications. Vouga M. and auth. (2014) conducted a retrospective analysis to evaluate the treatment of genital mycoplasma in 5377 pregnant patients showing symptoms of potential obstetric complications at 25–37 weeks of gestation. Women presenting with symptoms were routinely screened by culture for the presence of these bacteria and treated with clindamycin when positive. Compared with uninfected untreated patients, women treated for genital mycoplasma demonstrated lower rates of premature labour. Moreover, a reduction of neonatal complications rates was observed. Clearly, further research is needed.

In Belarus we use the following treatment regimens in pregnant women:

1. Azithromycin 500 mg orally 1 g once.
2. Josamycin 500 mg orally 3 times / day. The course is 10–14 days.
3. Erythromycin 500 mg orally 3 times / day. The course is 10 days.

3.3. GONORRHEA

Etiology/Pathogenesis. In the United States, an estimated 820,000 new N. gonorrhoeae infections occur each year. Gonorrhea is the second most commonly reported communicable disease. Urethral infections caused by N. gonorrhoeae among men can produce symptoms that cause them to seek curative treatment soon enough to prevent sequelae, but often not soon enough to prevent transmission to others. Among women, gonococcal infections are commonly asymptomatic or might not produce recognizable symptoms until complications (PID) have occurred. PID can result in tubal scarring that can lead to infertility and ectopic pregnancy. Annual screening for N. gonorrhoeae infection is recommended for all sexually active women aged < 25 years and for older women at increased risk for infection (those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI). Additional risk factors for gonorrhea include inconsistent condom use among persons who are not in mutually monogamous relationships, previous or coexisting sexually transmitted infections, and exchanging sex for money or drugs. Clinicians should consider the communities they serve and might opt to consult local public health authorities for guidance on identifying groups at increased risk. Gonococcal infection, in particular, is concentrated in specific geographic locations and communities. Subgroups of MSM are at high risk for gonorrhea infection and should be screened at sites of exposure (see MSM). Screening for gonorrhea in men and older women who are at low risk for infection is not recommended. A recent travel history with sexual contacts outside of the United States should be part of any gonorrhea evaluation.

Clinical manifistation. The manifestations of the disease are the same as in the non-pregnant state. If the infection takes place during pregnancy, it tends to be more acute.

Maternal complications. Infection increases the risk of preterm labor, PROM, intrapartum and postpartum infection. Disseminated infection includes: arthritis, meningitis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome).

Fetal/neonatal complications. The baby may be affected during labor while passing through the infected birth canal resulting in ophthalmia neonatorum.

Diagnosis. The diagnosis is to be confirmed by bacteriological identification of intracellular gram-negative diplococci from urethral or cervical smear. Serological test is to be done to exclude concurrent syphilitic infection.

Management. Pregnant women infected with N. gonorrhoeae should be treated with dual therapy consisting of ceftriaxone 250 mg in a single IM dose and azithromycin 1 g orally as a single dose. When cephalosporin allergy or other considerations preclude treatment with this regimen and spectinomycin is not available, consultation with an infectious-disease specialist is recommended Single dose injection of Ceftriaxone 125 mg IM or Cefixime 400 mg PO single

dose or a single 2 gm IM dose of spectinomycin is effective. Both the parents are treated. Ophthalmia neonatorum is treated with either silver nitrate or tetracycline preparation. Infected neonate is treated with single dose of ceftriaxone 50 mg/kg IM.

3.4. SYPHILIS

Etiology/Pathogenesis. Syphilis is a disease caused by the spirochete Treponema pallidum, which is transmitted by direct contact with an infectious moist lesion. These organisms can pass through intact mucous membranes or abraded skin or may be acquired transplacentally. A single sexual encounter with an infected partner carries 10 % chance of acquiring syphilis. Untreated, the disease progresses from primary to secondary to latent and, finally, to tertiary syphilis. Congenital syphilis has its own course and symptoms. There are 280,000 new cases of syphilis in the United States each year. The primary lesion of syphilis is the hard chancre, an indurated, firm, painless papule or ulcer with raised borders, which appears 10 days to 3 months (average is 3 weeks) after the treponemes have entered the body. The chancre may be located on the external genitalia, cervix, or vagina or any area of skin or mucous membrane of the body but is often not noted in women. The primary lesion persists for 1-5 weeks and is followed in most by spontaneous healing. Any lesion suspected of being a chancre should be subjected to darkfield examination, seeking treponemes, because culture is not available. Serologic tests for syphilis should be performed weekly for 6 weeks or until positive (usually reactive 1–4 weeks after the chancre appears).

Clinical manifistation. The generalized cutaneous eruption (macular, maculopapular, papular, or pustular) of secondary syphilis appears 2 weeks to 6 months after the primary lesion. The rash is a diffuse, bilateral, symmetric papulosquamous eruption that may involve the palms and soles. Perineal lesions (moist papules, condyloma latum) are present and positive for treponemes on darkfield examination or immunofluorescent studies. Other mucous patches may be present, as well as patchy alopecia, hepatitis, or nephritis. Generalized lymphadenopathy is typical. The secondary lesions last 2–6 weeks and heal spontaneously. Serologic tests are almost always positive at this stage. Latent syphilis is untreated syphilis after secondary symptoms have subsided. These patients remain infectious for 1–2 years and may have relapses resembling the secondary stage. Latency may be life-long or end with the development of tertiary syphilis, which occurs in one third of patients. Tertiary syphilis is marked by the presence of destructive lesions of skin, bone (gummas), cardiovascular system (aortic aneurysm or insufficiency), or nervous system disorders (meningitis, tabes dorsalis, paresis). Tertiary syphilis is fatal in 25 % of those affected. Although the maternal course of syphilis is unaltered by pregnancy, it is frequently not recognized unless detected by serologic screening. The treponemes may pass trans-

placentally throughout pregnancy, but if the disease is discovered and treated 18 weeks gestation, the fetus appears to suffer few sequelae. After 18 weeks, the classic signs of congenital syphilis occur in the fetus. The risk of fetal infection is greater during the secondary stage than during the primary or latent stages. The incidence of stillbirth and premature delivery is increased with syphilis. Hydramnios may be present. The placenta is involved; it has a waxy, hydropic appearance. Infection late in pregnancy results in fetal or neonatal infection in 40–50 %. Congenital syphilis occurs in the fetus or newborn whose mother has untreated syphilis. Depending on time of acquisition of infection, there may be signs of intrauterine infection (hepatosplenomegaly, radiographic changes in bone, anemia, jaundice, lymphadenitis, and meningitis) or the baby may appear unaffected, only to develop signs and symptoms equivalent to secondary syphilis sometime after birth. Classically, the newborn with congenital syphilis may be undergrown, with wrinkled facies because of reduced subcutaneous fat. The skin may have a brownish tint. The most common lesion of early congenital syphilis in the newborn is a bullous rash, so-called syphilitic pemphigus. Large blebs may appear over the palms and soles and, occasionally, in all other areas. Seropurulent fluid from the lesions swarms with treponemes. Mucositis identical with that of secondary syphilis in older patients may be noted in the mouth and upper respiratory passages of the newborn. The nasal discharge (syphilitic snuffles) is very infectious because it contains large numbers of T. pallidum.

The bones usually show signs of osteochronditis, and on X-ray, an irregular epiphyseal juncture (Guerin's line) is characteristic. Abnormalities of the eyes and other organs or the central nervous system may be apparent at birth, or defects may develop later in untreated cases. Any infant with the stigmata of syphilis should be placed in isolation until a definitive diagnosis can be made and appropriate treatment given. Because serologic testing evaluates IgG antibodies that are transplacentally acquired, the baby will be positive if the mother is positive. Effective neonatal treatment is shown by progressively falling titers over weeks to months.

Maternal complications. Depending upon the intensity and time of occurrence of the infiltration, the fate of the fetus will be as follows:

1. Abortion.
2. Preterm birth.
3. Intrauterine deaths leading to either a macerated or a fresh stillbirth.
4. Non-immune fetal hydrops (ascites, hepatomegaly).
5. Delivery of a highly infected baby with early neonatal death.
6. Survival with congenital syphilis.

Fetal/neonatal complications. Congenital infection results from transplacental migration of spirochete to the fetus. Congenital disease occurs with all stages of maternal infection and at any gestational age. The basic pathology is obliterative endarteritis. There is perivascular infiltration of lymphocytes and

plasma cells within the developing fetus. The placenta becomes bulky from increased connective tissue. The villi become bulky due to increased cellularity, the vascularity being diminished. Spirochete can hardly be found in the placenta. However, the baby may be affected without specific changes in the placenta.

Clinical features of congenital syphilis:

• Early: Maculopapular rash, rhinitis, hepatosplenomegaly, jaundice, lymphadenopathy, chorioretinitis and pneumonia.

• Late: Hutchinson teeth, deafness, saddle nose, shaber shins, hydrocephalus, mental retardation, clutton joint, interstitial keratitis and optic nerve atrophy.

If the baby is stillborn, spirochaetes may be detected from the fetal liver or spleen or from the intimal scraping of umbilical vein.

Diagnosis. Visualization of the treponemal organisms requires the presence of a moist cutaneous lesion for darkfield examination (fresh smear), immunofluorescent staining (dried smear), or silver staining for the treponemes in a biopsy specimen. Because the organisms are demonstrable for only a short time, diagnosis usually relies on history and serologic testing. Screening for syphilis is accomplished primarily by nonspecific nontreponemal antibody testing (e.g., VDRL, RPR). All pregnant women should be tested at the first visit. High-risk patients should be screened at 28–32 weeks gestation and at delivery. These tests become positive 3–6 weeks after infection. The titers are high in secondary syphilis and fall to low titers or even become negative in late syphilis. Titers that have a 4-fold drop or are falling in early syphilis indicate adequate treatment. False-positive tests may be associated with collagen disease, infectious mononucleosis, malaria, leprosy, febrile illnesses, vaccination, drug addiction, old age, and pregnancy itself. The titer seen with false-positive tests usually is low. However, any positive test should be investigated by an antitreponemal antibody test. The most widely performed antitreponemal antibody test is the fluorescent treponemal antibody absorption (FTA-ABS) test. The test remains positive regardless of therapy. Thus, titers are not determined. The differential diagnosis for primary syphilis includes chancroid, granuloma inguinale, lymphogranuloma venereum, herpes, carcinoma, scabies, trauma, lichen planus, psoriasis, drug eruption, aphthosis, mycotic infection, Reiter's syndrome, and Bowen's disease. The differential diagnosis for secondary syphilis includes pityriasis rosea, psoriasis, lichen planus, tinea versicolor, drug eruption, "id" eruptions, perleche, parasitic infection, iritis, neuroretinitis, condylomata accuminata, acute exanthems, infectious mononucleosis, alopecia, and sarcoidosis.

Serological test should be done as a routine in the first antenatal visit. VDRL (positive within 4 weeks of infection) is commonly done. A positive VDRL test has to be confirmed by fluorescent treponemal antibody absorption test (FTA-ABS) and Treponema pallidum micro hemagglutination (MHA-TP) test which are specific. Husband's blood should also be tested for VDRL. Detection of spirochaetes from the cutaneous lesion if any, by dark field examination.

Fetal infection could be diagnosed by polymerase chain reaction (PCR) of T. pallidum in amniotic fluid, fetal serum or spinal fluid. Spirochaetes may be detected from fetal liver or spleen.

Management. Treatment should be started as soon as the diagnosis is established. The baby may have the chance of protection even if the treatment is begun late in pregnancy. For primary or secondary or latent syphilis (< 1 year duration): benzathine penicillin 2.4 million units intramuscularly single dose. When the duration is more than a year — benzathine penicillin 2.4 million units IM weekly for 3 doses is given. If the patient is allergic to penicillin, oral azithromycin 2 gm as a single dose is given. Tertiary disease: Neurosyphilis — Aqueous crystalline penicillin G 18–24 million units IV daily for 10–14 days is given. If the treatment is given in early pregnancy, the treatment should be repeated in late pregnancy. Irrespective of the serological report, treatment should be repeated in subsequent pregnancies.

Obstetrics management. Treatment should be initiated if exposure has occurred even if evidence of disease is not present. During pregnancy, it is better to treat any suspicion of disease rather than risk congenital syphilis. Contacts and patients with early syphilis (primary, secondary and latent) should be treated with one of the following regimens:

1. Benzathine penicillin G 2.4 million units IM.

2. Tetracycline hydrochloride 500 mg PO qid or doxycycline 100 mg bid for 14 days (for penicillin allergy but not during pregnancy).

3. Erythromycin (stearate, ethylsuccinate, or base) 500 mg PO qid for 15 days (30 g total) for penicillin allergy and if unable to take tetracycline.

A short-lived (24 h) febrile reaction occurs in 50–75 % of those receiving penicillin therapy, presumably due to a release of toxic treponemal products. The fever, which occurs 4–12 h after injection, is a Jarisch-Herxheimer reaction. Congenital syphilis is treated with benzathine penicillin G 50,000 U/kg IM if the infant is asymptomatic and there is no evidence of neurosyphilis. Symptomatic congenital syphilis or neurosyphilis is treated with aqueous crystalline penicillin G 50,000 U/kg/day IV, divided in two doses for 10 days or aqueous procaine penicillin G 50,000 U/kg daily for 10 days.

3.5. BACTERIAL VAGINOSIS

Etiology/Pathogenesis. Bacterial vaginosis (BV) is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide producing Lactobacillus sp. in the vagina with high concentrations of anaerobic bacteria (e.g., Prevotella sp. and Mobiluncus sp.), Gardnerella. vaginalis, Ureaplasma, Mycoplasma, and numerous fastidious or uncultivated anaerobes.

BV is associated with having multiple male or female partners, a new sex partner, douching, lack of condom use, and lack of vaginal lactobacilli; women

who have never been sexually active are rarely affected. The cause of the microbial alteration that precipitates BV is not fully understood, and whether BV results from acquisition of a single sexually transmitted pathogen is not known. Nonetheless, women with BV are at increased risk for the acquisition of some STDs (e.g., HIV, N. gonorrhoeae, C. trachomatis, and HSV-2), complications after gynecologic surgery, complications of pregnancy, and recurrence of BV. BV also increases the risk for HIV transmission to male sex partners. Although BV-associated bacteria can be found in the male genitalia, treatment of male sex partners has not been beneficial in preventing the recurrence of BV.

Clinical manifistation. Some women experience transient vaginal microbial changes, whereas others experience them for longer intervals of time. Among women presenting for care, BV is the most prevalent cause of vaginal discharge or malodor; however, in a nationally representative survey, most women with BV were asymptomatic.

Maternal complications. Fetal/neonatal complications. Adverse pregnancy outcomes including premature rupture of membranes, preterm labor, preterm birth, intra-amniotic infection, and postpartum endometritis have been associated with symptomatic BV in some observational studies.

Diagnosis. BV can be diagnosed by the use of clinical criteria (i.e., Amsel's Diagnostic Criteria) or Gram stain. A Gram stain (considered the gold standard laboratory method for diagnosing BV) is used to determine the relative concentration of lactobacilli (long Gram-positive rods), Gram-negative and Gram-variable rods and cocci (G. vaginalis, Prevotella, Porphyromonas, and peptostreptococci), and curved Gram-negative rods (i.e., Mobiluncus) characteristic of BV. Clinical criteria require three of the following symptoms or signs:

1. Homogeneous, thin, white discharge that smoothly coats the vaginal walls.
2. Clue cells (e.g., vaginal epithelial cells studded with adherent coccoobacilli) on microscopic examination.
3. pH of vaginal fluid > 4.5.
4. A fishy odor of vaginal discharge before or after addition of 10 % KOH (i.e., the whiff test).

Detection of three of these criteria has been correlated with results by Gram stain. Other tests, including Affirm VP III (Becton Dickinson, Sparks, MD), a DNA hybridization probe test for high concentrations of G. vaginalis, and the OSOM BV Blue test (Sekisui Diagnostics, Framingham, MA), which detects vaginal fluid sialidase activity, have acceptable performance characteristics compared with Gram stain.

Although a prolineaminopeptidase card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is still underway. Detection of specific organisms might be predictive of

BV by PCR. Additional validation is needed before these tests can be recommended to diagnose BV. Culture of G. vaginalis is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity and specificity.

Management. Treatment is recommended for all symptomatic pregnant women. Studies have been undertaken to determine the efficacy of BV treatment among this population, including two trials demonstrating that metronidazole was efficacious during pregnancy using the 250 mg regimen; however, metronidazole administered at 500 mg twice daily can be used. One trial involving a limited number of participants revealed treatment with oral metronidazole 500 mg twice daily to be equally effective as metronidazole gel, with cure rates of 70 % using Amsel criteria to define cure. Another trial demonstrated a cure rate of 85 % using Gram-stain criteria after treatment with oral clindamycin. Multiple studies and meta-analyses have failed to demonstrate an association between metronidazole use during pregnancy and teratogenic or mutagenic effects in newborns. Although older studies indicated a possible link between use of vaginal clindamycin during pregnancy and adverse outcomes for the newborn, newer data demonstrate that this treatment approach is safe for pregnant women. Because oral therapy has not been shown to be superior to topical therapy for treating symptomatic BV in effecting cure or preventing adverse outcomes of pregnancy, symptomatic pregnant women can be treated with either of the oral or vaginal regimens recommended for non-pregnant women.

Obstetrics management. Treatment of BV in pregnant women can reduce the signs and symptoms of vaginal infection. A meta-analysis has concluded that no antibiotic regimen prevented preterm birth (early or late) in women with BV (symptomatic or asymptomatic). However, in one study, oral BV therapy reduced the risk for late miscarriage, and in two additional studies, such therapy decreased adverse outcomes in the neonate. Treatment of asymptomatic BV among pregnant women who are at high risk for preterm delivery (those with a previous preterm birth) has been evaluated by several studies, which have yielded mixed results. Seven trials have evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery: one showed harm, two showed no benefit, and four demonstrated benefit.

Similarly, data are inconsistent regarding whether treatment of asymptomatic BV among pregnant women who are at low risk for preterm delivery reduces adverse outcomes of pregnancy. One trial demonstrated a 40 % reduction in spontaneous preterm birth among women using oral clindamycin during weeks 13–22 of gestation. Several additional trials have shown that intravaginal clindamycin given at an average gestation of > 20 weeks did not reduce likelihood of preterm birth. Therefore, evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth.

Although metronidazole crosses the placenta, no evidence of teratogenicity or mutagenic effects in infants has been found in multiple cross-sectional and cohort studies of pregnant women. Data suggest that metronidazole therapy poses low risk in pregnancy.

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are less than those used to treat infections in infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable, but remain less than maternal plasma levels. Although several reported case series found no evidence of metronidazole-associated adverse effects in breastfed infants, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a single 2 g dose of metronidazole. Lower doses produce a lower concentration in breast milk and are considered compatible with breastfeeding. Data from studies of human subjects are limited regarding the use of tinidazole in pregnancy; however, animal data suggest that such therapy poses moderate risk. Thus tinidazole should be avoided during pregnancy.

3.6. TUBERCULOSIS

Etiology/Pathogenesis. The incidence ranges between 1–2 % amongst the hospital deliveries in the tropics, being confined predominantly to the underprivileged sectors of society. Incidence of tuberculosis is rising worldwide with the rising prevalence of HIV infected patients. In 2000, WHO showed the emergence of multidrug resistant tuberculosis (MDR-TB) all over the world. It is a "global health emergency". Positive family history or past history • Low socioeconomic status • Area with high prevalence of tuberculosis • HIV infection • Alcohol addiction • Intravenous drug abuse • Diabetes, jejunoileal bypass, under weight by > 15 %.

Clinical manifistation. Tuberculosis of the bronchi, lungs, and pleura is not directly affected by pregnancy. Tuberculous pregnant women are slightly more prone to spontaneous abortion and premature delivery than other women. Tuberculous endometritis is exceptional. Interruption of pregnancy because of pulmonary tuberculosis is almost never justified now that antituberculosis drugs are available.

Maternal complications. Provided the patient remains under medical supervision with adequate treatment, pregnancy has got no deleterious effect on the course of the disease; nor has the disease any adverse effect on the course of pregnancy. In active disease, fetus can be affected by transplacental route or by aspiration of amniotic fluid.

Fetal/neonatal complications. Infants born of tuberculous mothers are no more likely to develop the disease than others provided that they are separated from the infected mother and unfavorable environment at birth. Neonatal affection is mainly by postpartum maternal contact. In untreated patients, the incidence of preterm labor, IUGR and perinatal mortality is high.

Diagnosis

1. Tuberculin skin test with Purified Protein Derivative (PPD) when > 10 mm is considered positive specially in presence of risk factors.
2. X-ray chest (after 12 weeks).
3. Early morning sputum (three samples) for acid-fast bacilli.
4. Gastric washings.
5. Diagnostic bronchoscopy.
6. Extrapulmonary sites-lymph nodes, bones (rare in pregnancy).
7. Direct amplification tests for 16 S ribosomal DNA and gene probe can detect M. tuberculosis with greater sensitivity and specificity.

1. Congenital tuberculosis is diagnosed.
2. Lesion noted in the first week of life.
3. Infection of the maternal genital tract or placenta.
4. Cavitating hepatic granuloma diagnosed by percutaneous liver biposy at birth.

No evidence of postnatal transmission. Congenital tuberculosis is rare. Concomitant HIV infection increases the risk.

Management. However, it is important to discourage pregnancy in women with active tuberculosis and to maintain close medical supervision of those tuberculous women who do become pregnant. Institute follow up study of all women with a history of treated tuberculosis, and be alert to the possibility of reactivation of tuberculosis during each pregnancy. Advise deferring pregnancy (and prescribe contraception, if acceptable) until tuberculosis has been inactive for at least 2 years if minimal, 3 years if moderately advanced, and 5 years if far-advanced. In patients who have had tuberculosis, order chest x-rays after the fifth month, immediately after delivery, and 6 months after delivery

Women with active tuberculosis should receive the following drugs orally daily for a minimum period of 9 months.

Major thoracic surgery should be withheld, if possible, but if deemed necessary should be restricted to the first half of pregnancy beyond 12 weeks.

Breastfeeding: Breastfeeding is not contraindicated when a woman is taking anti-tuberculous drugs. Breastfeeding should be avoided if the infant is also taking the drugs (to avoid excess drug level). In active lesion, however, not only is breastfeeding contraindicated but the baby is to be isolated from the mother following delivery. Baby should be given prophylactic isoniazid 10–20 mg/kg/day for 3 months when the mother is suffering from the active disease. However, if the mother is on effective chemotherapy for at least 2 weeks, there is no need to isolate the baby. BCG should be given to the baby as early as possible.

Pregnancy is to be avoided until quiescence is assured for about two years. Spacing can be achieved by any methods acceptable to the couple. Oral contraceptives should be avoided when rifampicin is used. Due to accelerated drug metabolism contraceptive failure is high. A barrier method may be used. Puerperal sterilization should be seriously considered, if the family is completed.

Obstetrics management. Place of therapeutic termination: tuberculosis per se is not an indication for termination of pregnancy. Obstetric management is no different from other pregnant women, once tuberculosis is well managed. The management of the pregnant patient with tuberculosis requires the collaboration of the pulmonary physician and the obstetrician. The treatment of tuberculosis includes rest (physical and emotional), hospitalization if the disease is moderate or advanced, and chemotherapy. The reader is referred to other texts for details of treatment.

Prevention. Women (age < 35 years) with positive PPD and no evidence of active disease (asymptomatic) — Isoniazid prophylaxis 300 mg/day is started after the first trimester and continued for 6–9 months. Pyridoxin (Vit B6) 50 mg/day is added to prevent peripheral neuropathy. No major adverse fetal or neonatal effects are seen with these antituberculous drugs.

3.7. GROUP B STREPTOCOCCAL INFECTION

Etiology/Pathogenesis. Maternal infection with group B streptococcal infection (GBS) is an important cause of high perinatal mortality. Vaginal and anorectal colonization of GBS is the main source of infection. Main risk factors for neonatal infection are prolonged rupture of membranes, preterm labor, prolonged labor and low birth weight. Group B-hemolytic streptococcus, or Streptococcus agalactiae, is the most common bacterium associated with neonatal infection and the leading cause of life-threatening perinatal infections in the United States. A gram-positive encapsulated coccus that produces hemolysis on blood agar, GBS is responsible for an overall rate of neonatal infection of 1 to 3 per 1000 live births, 10 per 1000 deliveries in women colonized with GBS, and 40 to 50 per 1000 live births complicated by preterm delivery. Early onset neonatal GBS infection, which accounts for 80 to 85 % of all cases, is characterized by neonatal respiratory distress, apnea, pneumonia, and septic shock within 1 week of delivery. Confirmed by a positive blood culture, the infection has an overall mortality rate of 5 % (but the rate may be as high as 25 % among preterm infants), with surviving neonates often exhibiting significant long-term neurologic sequelae. By contrast, late-onset GBS infection usually results from community- or hospital-acquired (nosocomial) infections in preterm infants and presents as meningitis or sepsis more than 1 week after birth.

Transmission of early-onset neonatal GBS infection results almost exclusively during labor and delivery in parturients from lower genital or gastrointestinal tract colonization rather than transplacental passage. Not sexually transmitted, GBS is a commensal organism that intermittently colonizes the lower genital tract of 20 % (range, 15–40 %) of women at any one time. An estimated 8 to 10 % crossover of GBS carrier status exists during each trimester, and thus determination of GBS carrier status is not recommended at the first prenatal visit. Half of all infants born to women colonized with GBS will become colonized with GBS; however, most are asymptomatic.

A number of strategies have been proposed to prevent early onset GBS infection, including intrapartum maternal and postpartum neonatal antibiotic regimens. However, such antibiotic use has been associated with the emergence of antibiotic resistance an increased incidence of early-onset neonatal sepsis due to non-GBS organisms and maternal anaphylaxis (estimated as 1:60,000 for penicillin). 20 Because of these limitations, routine administration of GBS chemoprophylaxis is not recommended for all women in labor. Instead, two independent prophylaxis protocols have been proposed and deemed acceptable for select parturients by the American College of Obstetricians and Gynecologists (ACOG).

Clinical manifistation. In the mother, GBS can cause urinary tract infection, endometritis, and septicemia. There are several serotypes of GBS that cause human disease, and they can all be found in genital isolates; serotype III is the predominant cause of late-onset neonatal sepsis. Endometritis, UTI, PROM and preterm labor and wound infection. Diagnosis is made by culture of specimens obtained from vagina, perineum using a cotton swab. PCR can also be used. Currently universal cultures for all patients is recommended (CDC, 2002) for prevention of GBS infection. Intrapartum therapy with ampicillin 2 gm initially, then 1 gm 6 hourly is effective.

Maternal complications. GBS infections may cause:

1. Preterm rupture of the membranes and preterm labor.
2. Severe postpartum sepsis, particularly following Caesarean section.
3. Overwhelming neonatal sepsis that may lead to death.

About 20 % of women will carry group B streptococci in the vagina. About 2 % of these women will give birth to an infected infant and about 30 % of these could die from overwhelming sepsis. In maternal infection, GBS is often found to be one of multiple miscreant organisms. In chorioamnionitis, group B streptococcal isolates can be found in as many as 15 % of cases, often along with other organisms. Endometritis is similarly a polymicrobial infection, with similar culture rates to GBS. Group B streptococci can also be found in 2–15 % of infected post Cesarean section incisions. After Escherichia coli, GBS is the second most common bacteria found in maternal bacteremia, including cases of pyelonephritis. Clinical presentation of GBS infection can include a maternal fever and elevated white blood cell count. GBS has rarely been shown to cause fatal infections, necrotizing fasciitis, and maternal meningitis.

Fetal/neonatal complications. Neontal infections include R.D.S., pneumonia, jaundice, hypotension, septicemia and meningitis. Neonatal mortality is about 30–40 %. Early-onset disease occurs within 1 week of life (with most cases being identified within 72 h of birth), while late-onset disease occurs after the first week of life. Owing to the dramatic decline in early-onset disease in the 1990s, early- and late-onset disease now have similar occurrence rates, with case fatality rates of 4.7 % for the former and 2.8 % for the latter. 2 Survival is largely dependent upon gestational age

at birth, with 98% survival for greater than 37 weeks' gestation, 90 % for 34-36 weeks, and 70 % for infants less than 33 weeks old.

Risk factors for early-onset disease include maternal GBS colonization, prolonged rupture of membranes, preterm delivery, GBS bacteriuria during pregnancy, birth of a previous infant with invasive GBS disease, maternal clinical chorioamnionitis, young maternal age, African-American race, Hispanic ethnicity, and low levels of antibody to type-specific, capsular polysaccharide antigens. Colonization with GBS, preterm delivery, maternal race, and young maternal age are also independent risk factors for late-onset disease. There is an increased risk of long-term neurologic sequelae in late onset neonatal disease as up to one-third of these cases include neonatal meningitis.

Apart from neonatal disease, 9–15 % of stillbirths have been attributed to infection, with GBS isolated in a large number of these cases. This is especially true of early stillbirths, i.e., those that occur at less than 28 weeks' gestation, as opposed to term stillbirths.

Diagnosis. The optimal culture site for lower genital tract colonization has been rectovaginal. Recently, GBS has been isolated from vaginoperianal, anorectal, and perianal specimens with equalrates of positivity. To optimize yield, swabs from the rectogenital tract should be inoculated in selective growth media (commercially available) to suppress competing bacteria. However, blood agar is adequate for GBS recovery from endometrial, amniotic fluid, urine, and blood specimens. Rapid identification tests, including Gram stain, immuno-fluorescent antibody, colorimetric assay using starch serum media, and antigen detection (coagglutination, latex agglutination, enzyme immunoassay) all lack sufficient sensitivity or positive predictive value (PPV). Polymerase chain reaction (PCR) is a new technology that has not yet been widely implemented for rapid detection, but has been shown to be 97 % sensitive and 100 % specific, with a PPV of 100 % and a negative predictive value (NPV) of 98.8 %. 7 Under ideal conditions, test results have been available in 40-100 min. There are several limitations of PCR technology, including the inability to test for GBS sensitivity to various antibiotics, which is something that would be necessary in patients who have a history of anaphylaxis to penicillin. It is also unclear whether such rapid turnaround is adequate for routine use intrapartum, and whether all hospital laboratories can provide rapid results at night or at weekends. For now, screening should continue to rely upon genitorectal cultures as delinated in the 2002 Centers for Disease Control (CDC) guidelines.

Management. Fortunately, GBS continues to be susceptible to penicillin and ampicillin. However, as of 2003, 37 % of invasive GBS isolates were noted to be resistant to erythromycin and 17 % to clindamycin (Active Bacterial Core Surveillance/Emerging Infections Program Network, unpublished data). Resistance to cefoxitin, a second-generation cephalosporin, has also been detected.

In 2002, the CDC, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists produced new GBS chemoprophylaxis guidelines. These guidelines are predicated upon the GBS carrier status in the pregnant mother, which should have been obtained via a rectovaginal swab at approximately 36 weeks' gestation or within 5 weeks of delivery. In a circumstance in which one is testing a patient who has a history of penicillin allergy, especially anaphylaxis, upon obtaining a screening specimen, it is necessary to notify the laboratory to test for sensitivity to erythromycin and clindamycin if GBS is detected. Multistate data from 2003 showed a 34 % reduction in early-onset neonatal GBS disease incidence in the year following the issuing of these new guidelines.

For maternal infection, penicillin G is the drug of choice; this is usually administered at 5 million units intravenously initially, followed by 2.5 million units intravenously every 4–6h. For GBS prophylaxis intrapartum, the dosing interval should be 4h. In cases of shortage, as has been seen recently in the United States, ampicillin is a suitable alternative at 2g intravenously initially followed by 1g intravenously every 4–6h; again, note that intrapartum GBS prophylaxis necessitates dosing every 4h until delivery. In the case of chorioamnionitis, a polymicrobial condition, it is prudent to use broad-spectrum coverage that includes treatment for GBS and common Gram-negative organisms such as E. coli. Such an intrapartum regimen might be ampicillin (2 g i.v. every 6h) along with gentamicin (1.5 mg/kg i.v. every 8h). Treatment should be initiated as soon as the diagnosis is made, as intrapartum therapy will treat the fetus and reduce neonatal sepsis.

Postpartum endometritis is similarly a polymicrobial infection and deserves broad-spectrum treatment, preferably with i.v. antibiotics. Coverage should include anaerobic organisms and, hence, a triple antibiotic regimen of ampicillin, clindamycin, and gentamicin is commonly used. For neonates suspected of having GBS sepsis, empiric treatment is initiated with i.v. ampicillin and i.v. aminoglycoside to provide coverage similar to that offered in the treatment of chorioamnionitis. If there is bacteremia without meningitis, the treatment is extended to 48–72h. In the case of GBS as the sole isolate, then i.v. penicillin G is administered to complete a 10-day course of antibiotics. In the case of meningitis, i.v. ampicillin and gentamicin are administered until cerebrospinal fluid is sterile; i.v. penicillin G is continued to complete a 14-day course of antibiotic treatment.

Obstetrics management. Screening all pregnant women for the infection is not practical. All women presenting with preterm rupture of the membranes should have a sample of the amniotic fluid sent to identify the organism. If present, the baby should be delivered immediately with penicillin cover. A woman who is known to be a carrier for bHS should be given prophylactic i.v. penicillin during labour.

4. PARASITIC AND PROTOZOAL INFESTATIONS

4.1. TOXOPLASMOSIS

Etiology/Pathogenesis. Toxoplasmosis is a protozoan infestation caused by Toxoplasma gondii. Infection is transmitted through encysted organism by eating infected raw or uncooked meat or through contact with infected cat feces.

The prevalence of toxoplasmosis varies throughout the world, and is dependent upon the geographic location and age of the population under consideration. Hot, arid climates are associated with low prevalence; in the United States and Europe, the prevalence, based on serologic status, increases with age and exposure. Infection during pregnancy also varies by geography; acute antenatal infection occurs in 10 in 1000 pregnancies in France, 12 whereas it occurs in only 1.1 in 1000 pregnancies in the United States.13 The incidence of congenital infection is between 1 in 10000 to 10 in 10000 live births in the United States, or approximately 400–4000 births per year. 14 It is believed that half of these congenital infections are due to the consumption of contaminated meat. 14 Fetal infection only occurs with acute maternal toxoplasmosis. The likelihood of transmission and the severity of risk to the fetus vary with gestational age. Congenital toxoplasmosis is more frequent, but usually less apparent, when maternal infection occurs in later gestations. In France, Desmonts and Couvreur found that 17 % of first-trimester pregnancies with acute maternal toxoplasmosis, 24 % of the second-trimester pregnancies, and 62 % of the third-trimester pregnancies resulted in infected infants at a time before treatment was available. However, severe infections or stillbirths occurred in 75 % of the cases in the first trimester, 20 % in the second trimester, and 0 % in the third trimester.

Toxoplasmosis, a multisystem disease caused by the protozoan Toxoplasma gondii (T. gondii), is a serious threat to the fetus. Serologic evidence of T. gondii infection is present in almost 25 % of women in the United States. Most cases are chronic and probably pose little risk to the fetus. The acute case may lead to fetal infection with marked sequelae. The major vector in the United States remains unclear. The infection may be obtained from consumption of undercooked meat. Cats have been overemphasized as a vector. Only about 1 % of cats hunting and consuming rodents harboring T. gondii are infected. If infection occurs, the cat sheds oocytes in the feces for only about 2 weeks. During this time, human inoculation must occur by hand-to-mouth contact of cat fecal material. Toxoplasmosis, usually asymptomatic in adults, resembles cytomegalovirus disease in the infant. Severe perinatal toxoplasmosis is associated with growth retardation, microcephalus or hydrocephalus, microphthalmia, chorioretinitis, central nervous system calcification, thrombopenia, jaundice, fever, and death.

Clinical manifistation. Maternal complications. Maternal infection is rarely diagnosed clinically. Acute infection is diagnosed by detecting IgM specific antibody, high level of IgG antibody titre and detection of seroconversion for IgG

from negative to positive. Routine screening is usually not done. Chronic maternal toxoplasmosis is not considered to be a significant cause of recurrent abortion as parasitemia will not be repeated in subsequent pregnancies.

An immunocompetent adult with acute toxoplasmosis is often only minimally symptomatic or completely asymptomatic. When the disease is clinically apparent, symptoms similar to infectious mononucleosis, including malaise, myalgias, sore throat, and fever, may be present. Painful, but nonsuppurative, lymph node enlargement, most commonly involving the posterior cervical lymph nodes, is a frequent finding in acute toxoplasmosis. Other associated findings include maculopapular rash, hepatosplenomegaly, and lymphocytosis. Ocular symptoms such as blurred vision, photophobia, and eye pain may be present with chronic disease. In the immunocompromised patient, severe disease with pulmonary and central nervous system involvement can be seen.

Fetal/neonatal complications. It can also be acquired across the placenta. The fetal risk of infection increases with duration of pregnancy and is approximately 15 %, 30 % and 60 % in the first, second and third trimesters respectively. The fetus is only at risk if the mother is seronegative.

Risk of fetal damage decreases from 60 % in first trimester to almost zero percent at the end of pregnancy. There is increased rate of abortion, IUGR and stillbirth. During parasitemia, transplacental infection to the fetus occurs. The affected baby may develop hydrocephalus, chorioretinitis, cerebral calcification, microcephaly and mental retardation. Presence of IgM antibody in the neonates indicates congenital infection. IgG transmitted from the mother persists for many years.

Some investigators have reported an increased incidence of spontaneous abortion and preterm delivery in acute primary toxoplasmosis. Clinical manifestations that may prompt suspicion of infection include intrauterine growth restriction, nonimmune hydrops, hydrocephaly, microcephaly, anencephaly, and hydrancephaly. Ultrasound often fails to identify fetuses affected in utero. If ultrasonographic findings are present, they may include intracranial calcifications, ventricular dilation, hepatic enlargement, ascites, and increased placental thickness.

The most common finding is a normal infant. In fact, more than half of infants with congenital toxoplasmosis have no signs or symptoms in the newborn period. Chorioretinitis is the most common abnormal finding. The classic triad of periventricular calcifications, chorioretinitis, and hydrocephaly is actually uncommon. Other findings can include growth restriction, low birthweight, hydrocephalus, microcephaly, intracranial calcifications, jaundice, hepatosplenomegaly, cataracts, microphthalmia, strabismus, blindness, epilepsy, psychomotor or mental retardation, petechia secondary to thrombocytopenia, anemia, maculopapular rash, pneumonia, vomiting, and diarrhea. 20 Serious long-term complications include mental retardation, severe visual deficits, and seizures. Ad-

verse sequelae have been detected in long-term follow-up of infants with subclinical infection at birth.

Diagnosis. Routine antenatal screening for antibodies to T. gondii has been recommended. The Sabin-Feldman dye test and the indirect immunofluorescence test are diagnostic of toxoplasmosis. Both tests give positive results 2–3 weeks after infection and for years there-after. Thus, without sequential tests, an acute infection cannot be distinguished from a chronic one. The diagnosis of toxoplasmosis in a newborn is supported by elevated IgM in cord blood.

Detection can be achieved via direct and indirect methods. Indirect techniques should be used in immunocompetent patients, as these methods rely upon serologic analysis, specifically the detection of organism-specific IgG and IgM antibodies. Direct detection is with PCR, hybridization, isolation, and histology, and is largely reserved for diagnosis in immunocompromised individuals.

Detection of IgG and IgM antibodies should be performed in pregnant women who are suspected of having had toxoplasmosis exposure. IgM can appear as early as 1 week after an acute infection, increases rapidly, and then wanes, persisting for several weeks to months; in rare circumstances, IgM may even persist for years. IgG does not appear until several weeks after the IgM increase, but low titers usually persist for years. Traditionally, the Sabin-Feldman dye test, indirect fluorescent assays, indirect hemagglutination assays, and complement fixation tests have been used. More recently, enzyme-linked immunosorbent assay (ELISA), IgG avidity test, and agglutination and differential agglutination tests have been used for the detection of IgG antibodies. Most laboratories no longer use the Sabin-Feldman dye test. Avidity, i.e., functional affinity, testing of IgG antibodies is now routinely performed to help to distinguish acute from chronic infection. High-avidity antibodies are not seen in cases of infections acquired in the most recent 3-4 months. The differential agglutination (AC/HS) test is useful in distinguishing between a probable acute or chronic infection in pregnant women. The presence of Toxoplasma-specific IgG would indicate protection from further infection. The presence of a high Toxoplasma IgG titer with the presence of IgM is suggestive of a recent infection, especially if the IgM titer is high, but it must be remembered that IgM may persist for months or even years in some instances following acute infection. A negative IgM test, if found within the first 24 weeks of gestation, especially if associated with low titers of IgG, essentially rules out an acute infection during gestation and points to a chronic infection antedating conception. However, a negative IgM titer in the third trimester does not negate the possibility of an acute infection in the first trimester with a subsequent decline. In this circumstance, additional testing, such as IgG avidity testing as explained above, can be helpful. Finally, women who test positive for IgM antibody in a nonreference laboratory should always undergo confirmatory testing in a reference laboratory, as 60 % of these women are actually found to be chronically infected.

Prenatal diagnosis of congenital toxoplasmosis is possible. Initially, ultrasound, cordocentesis, and amniocentesis were recommended. Serologic tests for specific IgM and IgG were performed on fetal blood, as were nonspecific tests, including white blood cell count and hepatic enzymes. Also, there was isolation of the organism by inoculation into mice. However, IgM-specific antibodies may not be detected even in cultureproven cases because antibody synthesis may be delayed in the fetus and neonate. Isolation of parasites may also be unsuccessful because parasitemia may be intermittent, and the samples of fetal blood or amniotic fluid may be limited in quantity. More recently, prenatal diagnosis using PCR technology on amniotic fluid obtained by amniocentesis has essentially eliminated the need for periumbilical fetal blood sampling or serologic testing of amniotic or fetal specimens as this approach has greater sensitivity and is simpler. Sensitivity for PCR analysis of amniotic fluid depends on gestational age, but overall has a rate of 64 % (and in some studies has been noted to be as high as 98.8 %), with a specificity of 100 %, a PPV of 100 %, and a NPV of 87.8 %.

Management. Obstetrics management. Treatment of toxoplasmosis during pregnancy is problematic. Pyrimethamine currently is the drug of first choice against T. gondii. This drug, however, may be teratogenic, especially during the first trimester. If the newborn is treated with pyrimethamine, folinic acid supplementation will be required to reduce the toxicity of the drug. Sulfadiazine often is used additionally. Sulfonamide therapy is effective but must be discontinued before delivery. Sulfonamide drugs have a greater albumin-binding affinity than bilirubin, which may rise after delivery to critical levels. Even exchange transfusion of the newborn may be necessary to avoid kernicterus. A cat should not be a hazard if minimal precautions are taken -frequent handwashing and occasional soaking of litter boxes with ammonia solution. Pregnant women should cook meat well or freeze meat for at least 4 h before consumption to destroy T. gondii tissue cysts. Women at high risk for toxoplasmosis (e.g., veterinarians, butchers, or those with many cats) should be screened periodically for the disease.

Toxoplasmosis is a self limited illness in an immunocompetent adult and does not require any treatment. Pyrimethamine 25 mg orally daily and oral sulfadiazine 1 gm four times a day is effective. Luncovorin is added to minimize toxicity. Four to six weeks course is usually given. Pyrimethamine is not given in the first trimester. Spiramycin (3 gm orally daily) has also been used as an alternative. Acute toxoplasmosis during pregnancy is treated with spiramycin. Extended courses may be needed in an immunocompromised patient to cure infection. Treatment to the mother reduces the risk of congenital infection and the late sequelae.

Prevention. In some European countries, large-scale seroscreening and specific therapy are used to prevent congenital toxoplasmosis. The efficacy of medication is approximately 50 % in reducing congenital infection. If acute maternal toxoplasmosis is contracted between 2 and 10 weeks' gestation or if there

are major lesions documented by ultrasound, the option of termination should be discussed. The primary method of prevention of congenital toxoplasmosis is the application of certain hygienic measures. The pregnant woman should be advised to wash her hands thoroughly after contact with raw meat, cats, and materials potentially contaminated by cat feces. She should also eat meat only when it has been cooked to more than 66 °C. The brown color of well-done meat is due to myoglobin turning to metmyoglobin at this temperature, which is also the temperature at which the cysts are rendered noninfectious. It is too early to tell whether a primary prevention program will significantly reduce the incidence of acquired toxoplasmosis. A prospectively evaluated prevention program reduced the rate of seroconversion by 34 %, but this was not statistically significant.

4.2. TRICHOMONIASIS

Etiology/Pathogenesis. Trichomoniasis is the most prevalent nonviral sexually transmitted infection in the United States, affecting an estimated 3.7 million persons. Health disparities persist in the epidemiology of Trichomonas vaginalis (T. vaginalis) infection in the United States: 13 % of black women are affected compared with 1.8 % of non-Hispanic white women. T. vaginalis infection affects > 11 % of women aged ≥ 40 years, and particularly high prevalence has been detected among STD clinic patients (26 % of symptomatic women and 6.5 % asymptomatic women tested) and incarcerated persons (9–32 % of incarcerated women and 2–9 % of incarcerated men). The prevalence of trichomoniasis in MSM is low.

Clinical manifistation. However, most infected persons (70–85 %) have minimal or no symptoms, and untreated infections might last for months to years.

The leukorrhea is characterized as thin, yellow-green, and occasionally frothy, with a fetid odor. The discharge has a pH of 5-6.5. On saline wet mount, the unicellular flagellate may be observed moving about in a field of many leukocytes. The trichomonads are pear shaped and smaller than epithelial cells but larger than white cells.

Maternal complications. T. vaginalis infection in pregnant women is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, with two- to threefold increased risk for preterm delivery, and delivery of a low birthweight infant.

Fetal/neonatal complications. Although perinatal transmission of trichomoniasis is uncommon, treatment also might prevent respiratory or genital infection of the newborn.

Diagnosis. The use of highly sensitive and specific tests is recommended for detecting T. vaginalis. Among women, NAAT is highly sensitive, often detecting three to five times more T. vaginalis infections than wet-mount microscopy, a method with poor sensitivity (51–65 %). The APTIMA T. vaginalis assay (Hologic Gen-Probe, San Diego, CA) is FDA-cleared for detection of T.

vaginalis from vaginal, endocervical, or urine specimens from women. This assay detects RNA by transcription-mediated amplification with a clinical sensitivity of 95.3–100 % and specificity of 95,2–100 %.

Among women, vaginal swab and urine have up to 100 % concordance. Other FDA-cleared tests to detect T. vaginalis in vaginal secretions include the OSOM Trichomonas Rapid Test, an antigen-detection test using immunochromatographic capillary flow dipstick technology that can be performed at the point of care, and the Affirm VP III (Becton Dickinson, Sparks, MD), a DNA hybridization probe test that evaluates for T. vaginalis, G. vaginalis, and Candida albicans. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, with sensitivity 82–95 % and specificity 97–100 %. Self-testing might become an option, as a study of 209 young women aged 14–22 years found that > 99 % could correctly perform and interpret her own self-test using the OSOM assay, with a high correlation with clinician interpretation. The results of the Affirm VP III are available within 45 minutes. Sensitivity and specificity are 63 % and 99.9 %, respectively, compared with culture and TMA; sensitivity might be higher among women who are symptomatic. Neither the OSOM nor the Affirm VP III test is FDA-cleared for use with specimens obtained from men.

Culture was considered the gold standard method for diagnosing T. vaginalis infection before molecular detection methods became available. Culture has a sensitivity of 75–96 % and a specificity of up to 100 %. In women, vaginal secretions are the preferred specimen type for culture, as urine culture is less sensitive. In men, culture specimens require a urethral swab, urine sediment, and/or semen. To improve yield, multiple specimens from men can be used to inoculate a single culture.

The most common method for T. vaginalis diagnosis might be microscopic evaluation of wet preparations of genital secretions because of convenience and relatively low cost. Unfortunately, the sensitivity of wet mount is low (51–65 %) in vaginal specimens and lower in specimens from men (e.g., urethral specimens, urine sediment, and semen). Clinicians using wet mounts should attempt to evaluate slides immediately because sensitivity declines as evaluation is delayed, decreasing by up to 20 % within 1 hour after collection. When highly sensitive (NAAT) testing on specimens is not feasible, a testing algorithm (wet mount first, followed by NAAT if negative) can improve diagnostic sensitivity in persons with an initial negative result by wet mount. Although T. vaginalis may be an incidental finding on a Pap test, neither conventional nor liquid-based Pap tests are considered diagnostic tests for trichomoniasis, because false negatives and false positives can occur.

Management. Obstetrics management. Clinicians should counsel symptomatic pregnant women with trichomoniasis regarding the potential risks for and benefits of treatment and about the importance of partner treatment and condom use in the prevention of sexual transmission. Although metronidazole

treatment produces parasitologic cure, certain trials have shown no significant difference in perinatal morbidity following metronidazole treatment. One trial suggested the possibility of increased preterm delivery in women with T. vaginalis infection who received metronidazole treatment, yet study limitations prevented definitive conclusions regarding the risks of treatment. More recent, larger studies have shown no positive or negative association between metronidazole use during pregnancy and adverse outcomes of pregnancy. If treatment is considered, the recommended regimen in pregnant women is metronidazole 2 g orally in a single dose. Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment. Treatment of T. vaginalis infection can relieve symptoms of vaginal discharge in pregnant women and reduce sexual transmission to partners.

The benefit of routine screening for T. vaginalis in asymptomatic pregnant women has not been established. However, screening at the first prenatal visit and prompt treatment, as appropriate, are recommended for pregnant women with HIV infection, because T. vaginalis infection is a risk factor for vertical transmission of HIV. Pregnant women with HIV who are treated for T. vaginalis infection should be retested 3 months after treatment. Although metronidazole crosses the placenta, data suggest that it poses a low risk to pregnant women. No evidence of teratogenicity or mutagenic effects in infants has been found in multiple cross-sectional and cohort studies of pregnant women. Women can be treated with 2 g metronidazole in a single dose at any stage of pregnancy. Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are lower than those used to treat infections in infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable, but remain less than maternal plasma levels. Although several reported case series found no evidence of adverse effects in infants exposed to metronidazole in breast milk, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a single 2 g dose of metronidazole. Maternal treatment with metronidazole (400 mg three times daily for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods of time. Data from studies involving human subjects are limited regarding use of tinidazole in pregnancy; however, animal data suggest this drug poses moderate risk. Thus, tinidazole should be avoided in pregnant women, and breastfeeding should be deferred for 72 hours following a single 2-g dose of tinidazole.

5. FUNGAL INFECTATIONS

5.1. VULVOVAGINAL CANDIDIASIS

Etiology/Pathogenesis. VVC usually is caused by C. albicans but can occasionally be caused by other Candida sp. or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. None of these symptoms is specific for VVC. An estimated 75 % of women will have at least one episode of VVC, and 40–45 % will have two or more episodes. VVC occurs frequently during pregnancy. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated. Approximately 10–20 % of women will have complicated VVC, requiring special diagnostic and therapeutic considerations.

Clinical manifistation. The usual symptomatology includes vaginal discharge, vulvar pruritus, burning, and dyspareunia. Candida vaginitis commonly leads to dermatitis of the vulva and thighs. Symptomatology generally begins in the premenstrual phase of the cycle, but 20 % of women with Candida are asymptomatic. Unlike bacterial or protozoal vaginitis, Candida infections are not considered a sexually transmitted disease and are not commonly associated with mixed infections or sexually transmitted diseases. At particular risk for developing candidiasis are diabetics, oral contraceptive users, those who have recently taken antibiotics, and pregnant women. Recurrent Vulvovaginal Candidiasis (RVVC), usually defined as four or more episodes of symptomatic VVC within 1 year, affects a small percentage of women (< 5 %). The pathogenesis of RVVC is poorly understood, and most women with RVVC have no apparent predisposing or underlying conditions. C. glabrata and other nonalbicans Candida species are observed in 10–20 % of women with RVVC. Conventional antimycotic therapies are not as effective against these nonalbicans species as against C. albicans.

Diagnosis. A diagnosis of Candida vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, and thick curdy vaginal discharge. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either 1) a wet preparation (saline, 10 % KOH) or Gram stain of vaginal discharge demonstrates budding yeasts, hyphae, or pseudohyphae or 2) a culture or other test yields a positive result for a yeast species. Candida vaginitis is associated with a normal vaginal pH (< 4.5). Use of 10 % KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with KOH preparation should be performed for all women with symptoms or signs of VVC, and women with a positive result should be treated. For

those with negative wet mounts but existing signs or symptoms, vaginal cultures for Candida should be considered. If Candida cultures cannot be performed for these women, empiric treatment can be considered. Identifying Candida by culture in the absence of symptoms or signs is not an indication for treatment, because approximately 10–20 % of women harbor Candida sp. and other yeasts in the vagina. PCR testing for yeast is not FDA-cleared; culture for yeast remains the gold standard for diagnosis. VVC can occur concomitantly with STDs. Most healthy women with uncomplicated VVC have no identifiable precipitating factors. Vaginal cultures should be obtained from women with complicated VVC to confirm clinical diagnosis and identify unusual species, including nonalbicans species. C. glabrata does not form pseudohyphae or hyphae and is not easily recognized on microscopy. Although C. albicans azole resistance is possibly becoming more common in vaginal isolates, susceptibility testing is usually not warranted for individual treatment guidance.

Management. Obstetrics management. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women. Recommended Regimens: Over-the-Counter Intravaginal Agents: Clotrimazole 1 % cream 5 g intravaginally daily for 7–14 days; Clotrimazole 2 % cream 5 g intravaginally daily for 3 days; Miconazole 2 % cream 5 g intravaginally daily for 7 days; Miconazole 4 % cream 5 g intravaginally daily for 3 days; Miconazole 100 mg vaginal suppository, one suppository daily for 7 days; Miconazole 200 mg vaginal suppository, one suppository for 3 days; Miconazole 1,200 mg vaginal suppository, one suppository for 1 day; Tioconazole 6.5 % ointment 5 g intravaginally in a single application.

Prescription Intravaginal Agents: Butoconazole 2 % cream (single dose bioadhesive product), 5 g intravaginally in a single application; Terconazole 0.4 % cream 5 g intravaginally daily for 7 days; Terconazole 0.8 % cream 5 g intravaginally daily for 3 days; Terconazole 80 mg vaginal suppository, one suppository daily for 3 days.

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(на английском языке)

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