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CHAPTER 47

Infections in Pregnancy

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INTRODUCTION AND SIGNIFICANCE

Maternal and infant morbidity and mortality are obvious consequences of many intrapartum and peripartum infections, but even infections that produce few observable maternal symptoms can dramatically affect fetal intra-uterine growth and development.

Despite advances in peripartum care, maternal morbidity and mortality associated with infections in pregnancy are increasing even in developed countries. Recently published data[1,2] from the Center for Disease Control's Pregnancy Mortality Surveillance System indicates that although maternal mortality from hemorrhage, embolism, and anesthesia has declined in the United States, the proportion of maternal deaths due to infections has increased. During 1991–7 infection accounted for 13.2% of pregnancy-related deaths overall and 36.3% of abortion-related deaths. The greatest infection risk is found in blacks, older women, women without prenatal care,[1] and women with multiple pregnancy.[2] In the United States pregnancy rates are stable or increasing in these groups.[3]

Infection is also a major cause of morbidity and mortality for the fetus and newborn. Many perinatal infections are associated with intra-uterine growth retardation and low birthweight, or cause fetal and neonatal brain injury.[4] Infections, particularly bacterial vaginosis and chorioamnionitis, can result in preterm delivery of live-born infants (delivery before 37 weeks gestation), or stillbirth. Evidence of intra-uterine infection has been reported in up to 70% of spontaneous births occurring at less than 30 weeks gestation, and 30–40% after that time.[5] Notably, the rate of preterm birth in developed countries is rising, and in the United States increased from 9.5% in 1981, to 12.7% in 2005.[6]

In developed countries, infections due to *Treponema pallidum* (syphilis), *Toxoplasma gondii*, *Listeria monocytogenes*, parvovirus B19, HIV, group B streptococcus, *Mycoplasma* spp., *Ureaplasma urealyticum*, *Chlamydia trachomatis*, and other organisms associated with chorioamnionitis may cause stillbirth in up to 15% of pregnancies overall, with the greatest risk earlier in pregnancy. Among stillbirths at less than 28 weeks gestation, infection was estimated to be the cause in 19%, in comparison with 8% for stillbirths between 28 and 36 weeks, and 2% for stillbirths at more than 37 weeks.[7] In the United States fetal mortality rates for less than 28 weeks gestation, the period most likely to be associated with infection, have not declined since 1990, and the 2003 rate (3.21/1000 live births + fetal deaths) was even greater than the 1985 rate (2.01/1000). Black women were at the highest risk. The highest rate, 13.9/1000 live births plus fetal deaths, occurred in black women.[8]

Globally, the World Health Organization estimates that perinatally acquired infection is responsible for more than 25% of deaths in newborns.[9]

MECHANISMS OF INCREASED SUSCEPTIBILITY TO INFECTION IN PREGNANCY

A multitude of immunologic, endocrinologic, metabolic, physiologic, and anatomic changes influence the likelihood and course of many infections during pregnancy. Some of these changes are intrinsic, and occur in all normal pregnancies, while others occur to varying degrees in normal and abnormal pregnancies.

Changes in Immune Function

Changes in the immune response to infection are an inadvertent byproduct of the alterations in maternal immune function that are essential in order to initiate and sustain pregnancy. In a normal pregnancy, the maternal immune system must allow implantation and subsequent development of a fetal 'hemi-allograft'. When evaluating

changes in immune response during pregnancy, there are two important caveats: first, that systemic changes reflected in the peripheral blood are not completely representative of the dominant local changes at the maternal–fetal interface; and, second, that immune function is dynamic, and can vary during the course of pregnancy. In particular, changes in the placenta reflect this variation.

'Type 1' to 'Type 2' Shift

The current concept of a 'type 1' to 'type 2' shift in maternal immune function during pregnancy is based on a model of changes in T-helper lymphocyte function initially proposed by Wegmann and colleagues, and subsequently modified to include more recently recognized facets of the immune response (Table 47.1). Examples of infections for which 'type 1' immunity has been shown to be protective include leishmaniasis, salmonellosis, listeriosis, mycobacterial infections, and infections with fungal organisms such as *Candida*, *Coccidioides*, *Cryptococcus*, and *Aspergillus*. Certain bacteria, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus agalactiae* (group B streptococcus), and *Streptococcus pyogenes* (Group A streptococcus), also engender a primarily 'type 1' response.[10]

Wegmann and coworkers hypothesized that functional maternal immunosuppression in pregnancy was the consequence of a shift from a T-helper 1 (Th1, IFN-γ-secreting cell) to a T-helper 2 (Th2, Interleukin-4–IL-4–secreting cell)- response.[11] The basis for this hypothesis included clinical observations, for example, changes in severity of some immune-mediated conditions during pregnancy, such as improvement of rheumatoid arthritis but worsening of systemic lupus erythematosis, and findings in women with recurrent miscarriage, and evidence from studies of pregnancy in inbred mice. Subsequently, secretion of the Th1-cytokine, IFN-γ, has been shown to promote phagocytosis and killing of intracellular pathogens, while IL-4 and related Th2-cell-produced cytokines such as IL-10 and IL-13 stimulate B cell proliferation, class switching, and antibody production. Thus, a shift from a Th1- to a Th2-dominant immune response correlates with increased susceptibility to viral and other intracellular pathogens such as *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, and *Leishmania*, as well as the increased antibody production and physiologic hypergammaglobulinemia seen in pregnancy.[10]

However, findings in normal early human pregnancy indicate there is also a generalized inflammatory response that appears necessary for successful implantation. Leukocytosis, increased monocyte priming and phagocytosis, production of the proinflammatory cytokines IL-6 and TNFα, and increased C-reactive protein are observed.[12] Endotoxin receptors are increased.[13] These findings are consistent with activation of the innate immune response, and contribute to the intact response to most extracellular bacteria, but increased susceptibility to endotoxin and Gram-negative sepsis observed in pregnancy.

The current understanding of immune responses in pregnancy also incorporates more recently recognized regulatory T cell subpopulations such as Th3, Tr1, and Treg cells,[14,15]

TABLE 47.1 'Type 1' to 'Type 2' shift in pregnancy

Cell type	Manifestations	Effect
T cells	↓ Th1 (IFN-γ-producing)	Suppression
	↑ Th2 (IL-4-producing)	
	↑ Treg	
NK cells	Peripheral blood	Suppression
	↓ IFN-γ, cytotoxic activity	
	↓ 'type 1'(decreased IL-18R + NK cells)	
	↑ 'type 2'(increased ST2L + NK cells)	
	Uterus	
	↑ NK3 cells (TGFβ-producing)	
Monocytes	↑ Numbers, phagocytosis, respiratory burst	'Alternative' activation
	↑ CD14 endotoxin receptor expression	
	↑ IL-12 secretion	
Granulocytes	↑ Numbers, phagocytosis, respiratory burst	Activation
Dendritic cells	↓ CD86, HLA-DR expression	Suppression
	↓ IL-12 production	
	↑ IL-10 production	

and the regulatory role of cells of the innate immune system, such as monocytes,[13] NK cells,[12,15] and dendritic cells.[16] Treg cells, which can inhibit allograft rejection, antitumor response, and contribute to persistence of intracellular pathogens such as *Leishmania*, express the CD25 cell marker. The number of circulating maternal Tregs increases throughout pregnancy, then slowly declines postpartum. Increased numbers of CD4 + CD25 + Treg cells are found in human maternal decidua, possibly in response to increased progesterone or other pregnancy hormones.[14]

Changes in the NK cell population also occur early, by the 12th week of pregnancy, and much earlier than the Th2 shift, which is more apparent in the third trimester. The 'type 1 to type 2 shift' in the NK cell population is evidenced by changes in cell markers including decreased IL-18 receptor expression, increased ST2L expression, and by decreased IFN-γ production;[12] the type 2, IL-10–producing but IFN-γ-nonproducing 'NK2' cells are increased.[15] A regulatory NK cell population important for allograft tolerance has recently been described, and there appears to be a similar role for regulatory NK cells in protecting the fetus. A unique, immunosuppressive population of regulatory NK cells has been reported in the uterus of pregnant women. These cells are recruited to the endometrium from the peripheral blood, and proliferate and differentiate to TGF-β-producing, immunosuppressive NK3 cells in the decidual microenvironment. These cells have an inhibitory receptor that recognizes placentally expressed class I antigens such as HLA-C, HLA-G, and HLA-E, to inhibit maternal NK cell activity.[15]

A shift in pregnancy to favor 'type 2' responses can also be demonstrated in circulating dendritic cells, and in monocytes and granulocytes. In pregnancy, CD86+, HLA-DR+ dendritic cells are decreased in the third trimester, and are biased to secrete IL-10 rather than IL-12, favoring a Th2 phenotype.[16] Monocytes and granulocytes, which are the primary effector cells of the innate immune system, increase in number beginning in the first trimester, and have an activated phenotype, as demonstrated in vitro by enhanced phagocytosis and respiratory burst activity. Monocyte expression of the endotoxin receptor CD14 is increased, as is the endotoxin-induced production of IL-12.[13] In late gestation, monocytes and granulocytes concentrate in the decidua, and increase production of cytokines. Cytokine expression is further increased in labor, and may act to promote labor. The underlying activation of granulocytes and monocytes, and their potential enhanced cytokine response to microbial pathogens, may explain the association between infection and preterm birth.

In a 'type 2' cytokine environment, monocyte activation is shifted from a 'classical' to an 'alternative' activation pattern When exposed to the type 2 cytokines IL-4, IL-10, and TGF-β, monocytes express receptors with broad specificity for foreign antigens, such as macrophage mannose receptor, resulting in increased endocytosis and antigen presentation. By contrast, functions enhanced by exposure to type 1 cytokines such as nitric oxide production, cytotoxicity and lysis of microorganisms, are reduced.[18] 'Alternatively-activated' monocytes can further promote the 'type 2' environment by inducing differentiation of naïve T cells into Th2 cells.

TABLE 47.2 Immunomodulating factors produced by the placenta

Cell receptors/antigens
• class I HLA-antigens, primarily HLA-G, but also HLA-C, HLA-E, HLA-F
• soluble HLA-G isoforms, primarily HLA-G5 and HLA-G6
• Toll-like receptors (TLRs)
Cytokines
• IL-10
• IL-4
• Macrophage colony-stimulating factor (M-CSF)
• Vascular endothelial growth factor (VEGF)
• IFN-γ
• Transforming growth factor-beta (TGFβ)
Hormones
• Progesterone
• Estradiol
• Corticotrophin releasing hormone
• Human placental lactogen
Syncytiotrophoblast debris/microparticles

Immune Modulation by the Placenta

Development of the placenta occurs concurrently with changes in the immune response, and the placenta plays a role as an immune-modulating organ. As the placenta develops, it changes not only structurally, but also in expression of glycoproteins, cytokines, and hormones, with related local and systemic effects on immune function (Table 47.2). Early in pregnancy, local effects predominate. One important feature of the placenta is its expression of unique class I HLA-antigens, primarily HLA-G, but also HLA-C, HLA-E, and HLA-F; the placenta does not produce HLA-A, HLA-B or HLA-D. HLA-G expression by trophoblast cells can be activated by IL-10, which also downregulates expression of the classical class I and II HLA antigens.

HLA-G interacts with uterine macrophages and NK cells to stimulate local production of angiogenic factors and cytokines including IFN-γ, and is immunosuppressive to CD8+ and CD4+ T cells.[12] The trophoblast also secretes the soluble isoforms HLA-G5 and HLA-G6, which can be detected in amniotic fluid and serum from women in all three trimesters.[19] These soluble isoforms have been shown to inhibit NK cell and CD8+ T cell-mediated lysis and to suppress CD4+ T cell proliferation in vitro (reviewed by Carosella[20,21]). HLA-G may also play a role in presentation

of viral antigens.[22] It is noteworthy that Herpes simplex virus and human cytomegalovirus can disrupt placental HLA-G expression.[22,23]

The placenta produces a number of cytokines that have local immunomodulatory effects, and can also enter the maternal circulation. These cytokines include the immunosuppressive, Th2-enhancing cytokines IL-4[24] and IL-10,[25] plus TGF-β,[26,27] which enhances generation of Tregs and alternative activation of monocytes. TGF-β1 has been found in amniotic fluid, and at increased levels in the blood of women between 21 and 36 weeks gestation.[28] Placentally produced cytokines that support monocyte activation include macrophage colony-stimulating factor, vascular endothelial growth factor, and pregnancy-specific glycoproteins such as PSG1a.[29]

Later in pregnancy, increased placental production of progesterone, estradiol, corticotrophin-releasing hormone, human placental lactogen, and other pregnancy-related hormones further contributes to the systemic Th1 to Th2 shift and to enhancement of the monocyte response (reviewed in Sacks[13]). The placenta also sheds syncytiothrophoblast debris, including subcellular microparticles that are released into the maternal circulation. In co-culture experiments, these microparticles stimulate PBMCs through monocyte and dendritic cell uptake, resulting in production of TNFα and IL-12, but minimal IL-18 or IFN-γ, and promoting the type 2 bias.[12]

Pregnancy-associated tissues, such as amniotic epithelial cells, decidual inflammatory cells, and placenta express toll-like receptors (TLRs), particularly TLR2, TLR4,[30] and TLR3.[31] The TLRs are pattern-recognition receptors that recognize repeating sequences on the surface of microorganisms. Expression of TLRs is inhibited by estrogen and enhanced by higher progesterone levels. Some evidence suggests that TLR2 expression is altered in placental samples in acute chorioamnionitis.[32] In cultures of cells derived from normal first-trimester trophoblast, cross-linking of TLR4 promotes cytokine expression, but ligation of TLR2 results in apoptotic cell death. One interpretation is that stimulation through TLRs could be a way in which intra-uterine infections lead to preterm labor, intra-uterine growth retardation, spontaneous abortion, and preeclampsia.[33] However, data regarding the role of these receptors in the context of pregnancy are still limited.

Endocrinologic and Metabolic Changes

Steroid Hormones

In pregnancy, increased levels of the steroid hormones cortisol, estrogen, and, in particular, progesterone, are found locally in the uterus and placenta and in the circulation.[34] These pregnancy-associated steroids modulate the generation, survival, and activity of various immune cells. Most of the available data come from murine models. In mice, pregnancy steroids induce thymic involution, marked by shrinkage of the cortex with loss of CD4 + CD8+ cells, and concurrent expansion of the medulla with production of Th2 cells (reviewed by Clarke and Kendall[35]). Progesterone has a major influence on lymphocyte production, acting through intracellular receptors in thymic epithelium,[36] and by downregulating production of B cells in the bone marrow.[37] Steroid hormones also decrease the number of circulating lymphocytes by inducing apoptotic cell death. Although there is limited direct evidence from human pregnancy, similar effects have been described in many other animals, suggesting these mechanisms are conserved.[38]

Glucocorticoids and progesterone influence the function of T lymphocytes by stimulating IL-4 and IL-10, but suppressing IFN-γ and IL-12 production.[39,40] In vitro, progesterone can influence even established Th1 clones to shift to produce Th2 cytokines.[41] Progesterone also acts indirectly by stimulation of progesterone-responsive tissues to produce P-induced blocking factor (PIBF), which induces production of the Th2 cytokines, leukemia inhibitory factor, and M-CSF, increases B cell antibody production, suppresses NK function, inhibits cytotoxicity by blocking degranulation and perforin release, and inhibits transformation into lymphocyte-activated killer cells.[42,43] Progesterone acts on the uterus to enhance homing of NK cells, and upregulates placental expression of HLA-G and TLRs.[33] Estrogens contribute to modulation of the immune response by stimulating proliferation of a different cell population, the CD4 + CD25+ Treg cells.[44] The steroid hormones also promote alternative activation of monocytes, and the shift towards antigen presentation and immune tolerance.[18] The impact of the changes in immune response due to progesterone and estrogen has been shown in several models. Pregnancy-related sex steroids have been shown to influence susceptibility to infection with *Listeria monocytogenes* and *Toxoplasma gondii* (reviewed by Roberts *et al.*[45]). In rodent models, higher estrogen levels or estrogen treatment increased susceptibility to *Neisseria gonorrhoeae*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*.[46,47] In mice, progesterone administration increases mortality from infection with herpes simplex virus type 2 (HSV-2). In rats, progesterone treatment before infection with *Chlamydia trachomatis* increases susceptibility to uterine infection, and prevents clearance of the organism resulting in a persistent infection; concurrent estrogen treatment limited the degree of inflammatory response.[48]

Other Pregnancy-Related Hormones

In addition to steroid hormones, a number of placental products including corticotrophin-releasing hormone, human chorionic gonadotropin, and human placental lactogen can also suppress lymphocyte function, and activate monocytes.[13] Prolactin, which increases during pregnancy, helps suppress cell-mediated immunity, augments B cell function and survival, in part through modulation of Th2 cytokines, and helps to mediate the effects of estrogen.[49] A relationship between prolactin levels and susceptibility to parasitic infections, particularly malaria, has been proposed.

Diabetes Mellitus

Diabetes mellitus (DM) in pregnancy may be pre-existing, either insulin-dependent (0.5%) or non-insulin dependent (2%), or may be gestational (3–6%) and a consequence of the pregnancy itself. Non-insulin-dependent and gestational diabetes both occur with greater frequency in non-whites.[50] Underlying hepatitis B infection has been reported as a risk for development of gestational DM even in women with low weight and body mass.[51] In pregnancy, circulating insulin antagonists including cortisol, prolactin, human placental lactogen, and leptin contribute to increased insulin resistance, with worsening of preexisting diabetes. Medical complications including infection are more frequent in pregnant women with diabetes, although most risk occurs in women with preexisting diabetes.[52]

Overall, there is a four-fold increased risk of infection pre-and post-partum in insulin-dependent diabetic pregnant women.[53] Examples of increased risk include colonization and infection with group B streptococcus and post-cesarean wound infections.[54,55] Unfortunately, the older literature does not always clearly distinguish between risk for pregnant women with preexisting DM and risk in women without DM prior to pregnancy, and increased risk cannot always be extrapolated for gestational diabetes. For example, solely gestational DM may not represent an increased risk for perinatal infection with group B streptococcus.[56]

By contrast, the risk of urinary tract infection, particularly due to Gram-positive organisms, is increased in pregnant women with both preexisting and gestational DM. The frequency of urinary tract infections is decreased by good glucose control.[57] The risk of periodontal disease is also increased in all diabetic pregnant women, with a rate of 4.8% to 9.0% in gestational diabetes, and an even higher prevalence of 30.5% in women with preexisting diabetes.[58]

Physiologic Changes

Uterine Decidual and Syncytiotrophoblast Production of IDO

The amino acid tryptophan appears to be an important proliferation signal for T lymphocytes. Tryptophan is metabolized by the enzyme indoleamine 2,3-dioxygenase (IDO). Increased IDO activity causes a local decrease in tryptophan, and a local suppression of Th1 activity. IDO is produced by tissue macrophages in response to IFN-γ, by dendritic cells in response to stimulation by Treg cells,[59] and by the decidua and the fetal syncytiotrophoblast.[60]

Gingival Hyperplasia

In pregnancy, increased estrogen, progesterone, and chorionic gonadotropin cause swelling of endothelial cells and pericytes in the gingival microvasculature, causing the gums to become soft, swollen, and hyperemic. Concurrently, there is a marked increase in the proportion of anaerobic species, particularly *Bacteroides melanogenicus*, *Prevotella intermedia*, and *Porphyromonas gingivalis.* As a consequence of these changes, pregnant women are more likely to develop gingivitis. Although the mechanism has not been elucidated, maternal peridontitis has been associated with preterm birth and low birthweight. The level of risk correlates with the severity of the periodontal disease (reviewed by Krejci[61]).

Anatomic Changes

Some of the anatomic changes that occur during pregnancy are associated with altered risk of infection. Most prominent among these are changes in the urinary tract and the development of pregnancy-specific tissues such as the placenta.

Urinary Tract

Asymptomatic bacteriuria occurs in 4–6% of both pregnant and non-pregnant women, but pregnancy-associated anatomic, functional, and hormonal changes in the urinary tract (Table 47.3) increase infection risk.[62–64] Many assessments of risk have used 100 000 colony forming units (CFU)/ml as the definition of bacteriuria for midstream urine specimens collected from asymptomatic patients; lower counts may be significant in patients with symptoms, or if urine is collected by catheterization, or for Gram-positive bacteria or yeast.

Glucosuria, increased urine pH due to bicarbonate excretion, stasis due to bladder muscle relaxation, and increased bladder volume encourage bacterial growth in the urine. In pregnancy, the risk of cystitis is 30–60% in women with asymptomatic bacteriuria when colony counts are $\geq$100 000 CFU/ml. After 20 weeks gestation, pyelonephritis is a common complication of UTI due to ureteral obstruction and urinary stasis. Dilatation of the ureters in response to hormonal changes such as increased progesterone, or possibly to estrogen or relaxin, is apparent in some women as early as the 7th week of gestation. Hormonal factors also cause decreased ureteral peristalsis, which may progress to intermittent atony in later pregnancy. Additional mechanical dilation of the ureters occurs in mid- and late pregnancy due to the enlarging uterus. The dilated ureters may contain over 200 ml of urine.[62] Dextro-rotation of the uterus places the right kidney at greater risk.[63]

The vast majority of UTI are caused by *Escherichia coli*, although Gram-positive pathogens are increased in women with DM. Treatment of asymptomatic bacteriuria decreases the risk of subsequent pyelonephritis to 1–4%.[65]

Respiratory System

Pregnancy causes a progressive decrease in the expiratory reserve volume and residual volume, and thus the functional reserve capacity and total lung capacity. Although these changes are not thought to increase the risk of contracting pneumonia, a decreased respiratory reserve increases the risk of respiratory failure and complications for mother and

TABLE 47.3 Anatomic and functional changes in the urinary tract and infection risk

	Alteration	Consequence
Kidney	↑ GFR	↑ Excretion of protein, amino acids, glucose
	↑ Renal plasma flow	↑ Urine output
	Glucosuria	May ↑ bacteriuria and UTI
	↑ Bicarbonate wasting	Compensatory respiratory alkalosis, may ↓ buffering capacity
Renal calyces and ureters	Progesterone-related dilation	Physiologic hydronephrosis and hydroureter in 80%, R > L
	Ureteral muscle relaxation	↓ Peristalsis
	Compression by the enlarging uterus	Postural urine flow in late pregnancy, ↑ susceptibility to pyelonephritis
Bladder	Smooth muscle relaxation, bladder atony	Urinary stasis and ↑ UTI risk
	Compression by the enlarging uterus	↑ bladder pressure,↑ vesicoureteral reflux and ↑ susceptibility to pyelonephritis

fetus.[66] Respiratory compromise from pneumonia decreases the maternal ability to meet the increased oxygen requirements needed to support a fetus. Additionally, the increased minute ventilation in pregnancy leads to a decreased $PaCO_2$ with a compensatory decreased serum bicarbonate (compensated respiratory alkalosis). As a consequence, even slight CO_2 retention is poorly tolerated, and may contribute to increased maternal morbidity and mortality from pneumonia, particularly during the third trimester.[67] In addition, the compensatory decrease in serum bicarbonate increases vulnerability to metabolic acidosis from sepsis or other causes.

Pneumonia caused by viral pathogens, particularly varicella, influenza, measles, and the coronavirus associated with severe acute respiratory syndrome (SARS), and by *Coccidioides immitis*, are associated with more severe outcomes in pregnant women. Bronchitis-bronchiolitis and pneumonia are also associated with a higher rate of preterm birth.[68] In the third trimester, relaxation of the gastroesophageal sphincter, delayed gastric emptying, and increased intra-abdominal pressure increases the risk of aspiration and aspiration-related pneumonia.

Placenta and other Pregnancy-Associated Tissues

The presence of the placenta and other pregnancy-associated tissues is a risk for certain infections, such as choriamnionitis, and for other infections associated with the puerperal period. The placenta can also be a focus of infection because of specific organism tropism, best described for *Plasmodium falciparum* malaria. When *P. falciparum* infection occurs in pregnancy, the parasite expresses specific proteins that mediate the binding of infected erythrocytes to chondroitin sulfate A produced by the placenta. Large numbers of parasitized erythrocytes can be sequestered in the placenta.

The placenta may also serve as a nidus for infection in listeriosis. Evidence from a guinea pig model indicates that, once infected, the placenta serves as a source for reseeding other maternal organs. In mammals, *L. monocytogenes* infection may be difficult to clear until the placenta is expelled.[69]

INFECTIONS FOR WHICH PREGNANCY ALTERS MATERNAL SUSCEPTIBILITY OR COURSE

Some infections occurring during pregnancy primarily have consequences for the mother, and only secondarily affect the fetus. These infections are unlikely to be transmitted to the fetus, and if promptly treated do not increase the likelihood of adverse outcome for the infant. Other pregnancy-associated infections that mostly affect the mother are those that occur during the puerperium, the period including labor and the following six weeks, and are a direct consequence of the birth process or its management.

Urinary Tract Infection

Cystitis occurs in 1–2 % of pregnancies. Although anatomic and physiologic changes increase the risk of urinary tract infection (UTI) in pregnant women, the major factor influencing the likelihood of infection is the presence of asymptomatic bacteriuria early in pregnancy. Other underlying conditions that concurrently increase the risk for UTI include insulin-dependent and non-insulin-dependent diabetes mellitus, the acquired immunodeficiency syndrome, and previous urologic abnormalities. Other reported risk factors include a history of previous UTI or

sickle cell hemoglobinopathy (early pregnancy) and lower socioeconomic and educational status, previous Chlamydial infection, and illicit drug use (after 20 weeks gestation).[62,70]

As in non-pregnant women, most UTIs are caused by gut flora, generally the Enterobactericeae and particularly *E. coli*, although Gram-positive pathogens are increased in women with DM. Treatment of asymptomatic bacteriuria dramatically decreases the risk of infection, and screening of women at 12–16 weeks gestation with a urine culture is recommended. The value of repeated screening is unknown, but the risk of UTI and pyelonephritis are reportedly very low in women with a negative initial culture.

In women with a positive culture, the current recommendations are to treat even in the absence of symptoms. Although single dose therapy has been used, with the exception of single dose fosfomycin, treatment for 3–7 days is more effective. After treatment, pregnant women should be screened periodically for recurrent bacteriuria.[71] The reported sensitivity of leukocyte esterase/nitrate dipsticks is very variable (50–92%) even in large studies,[72] suggesting that in this known high risk group screening by urine culture is preferable. A similar regimen and follow-up is recommended for women with bacteriuria who also have symptoms of cystitis such as frequency, urgency, and dysuria. Antibiotics recommended for treatment of UTI that are considered safe for use in pregnancy are listed in Table 47.4. Because of increasing resistance, treatment should be modified based on susceptibility results unless the bacteriuria has cleared with empiric therapy. Women with recurrent UTI may benefit from a single postcoital antibiotic dose, or may require daily suppression with nitrofurantoin or cephalexin. If group B streptococci are isolated, intrapartum penicillin prophylaxis is required even if the patient is screen negative at a later date.

Short-term antibiotic therapy is unlikely to have adverse effects on the fetus. Nitrofurantoin has been associated with hemolytic anemia in G-6-PD deficient women, and rarely with pneumonitis. Sulfonamides may be associated with hyperbilirubinemia, but this is unlikely to be significant during a short course of treatment.

Acute pyelonephritis follows UTI or asymptomatic bacteriuria in up to 25% of pregnant patients if untreated. Pyelonephritis is more likely in the second and third trimesters, but over 20% of cases occur in the first trimester.[73] Symptoms include fever and flank tenderness, often accompanied by rigors, nausea, vomiting, and costovertebral angle pain and tenderness, usually associated with pyuria. In pregnant women, pyelonephritis may be complicated by preterm labor, septic shock or acute respiratory distress syndrome,[70] possibly reflecting an increased sensitivity to endotoxin in pregnancy. Pulmonary injury is most likely to occur in sicker patients who have tachycardia and high fever, in cases of fluid overload, or when beta-agonists are given for tocolysis.[74] In a recent prospective series, pulmonary insufficiency occurred in 7% of pregnant women with pyelonephritis.[73] In general, pregnant women with pyelonephritis should be hospitalized for initial management, and monitored for development of these complications. Initial treatment should include intravenous antimicrobials and careful intravenous hydration, with modification of therapy based on culture results. Suggested initial regimens are listed in Table 47.4. Over 70% of infections are caused by *E. coli*. Gram-positive organisms, particularly group B streptococcus increase in importance in later pregnancy, and in some series cause more than 10% of infections in later pregnancy.[73]

Penicillin, ampicillin or amoxicillin should be used for treatment of infections caused by group B streptococci. Group B streptococci remain susceptible to penicillin, and testing is not needed except in cases of penicillin allergy, when susceptibility to clindamycin and erythromycin should be determined. By contrast, resistance in Gram-negative organisms is increasing, particularly to ampicillin and trimethoprim/sulfamethoxazole. A review of 3871 urine culture isolates from women aged 16–45 years collected from July 2005 through June 2008 in our Hospital Center indicated that >90% of enterococcal isolates were susceptible to ampicillin, and >84% of *S. aureus* isolates were methicillin-susceptible. By contrast, susceptibility of *E. coli* was only 53% to ampicillin, 70% to cephalothin and

TABLE 47.4 Antibiotic regimens for treatment of asymptomatic bacteriuria and UTI in pregnancy

	Antimicrobial
Asymptomatic bacteriuria and cystitis	Amoxicillin 500 mg orally three times/day
	Ampicillin 250 mg orally four times/day
	Cephalothin or cephalexin 250 mg orally four times/day
	Fosfomycin one 3 g sachet orally
	Nitrofurantoin 100 mg orally twice/day
	Trimethoprim/sulfamethoxazole 160/800 mg orally twice/day
Pyelonephritis	Ampicillin 2 g intravenously every 6 h
	Plus gentamicin 5–7 mg/kg intravenously once daily
	Cefazolin 1–2 g intravenously every 8 h
	Cefotaxime 1–2 g intravenously every 8 h
	Ceftriaxone 1–2 g intravenously once daily
	Ceftazidime 1–2 g intravenously every 8 h
Other agents	Amoxicillin/clavulanate 500 mg orally every 8 h
	Aztreonam 1–2 g intravenously every 6–8 h

trimethoprim/sulfamethoxazole, and 96% to nitrofurantoin. As might be expected, resistance in all cases was higher in isolates from women aged 31–45 years than from women aged 16–30 years. Of note, susceptibility to amoxicillin/clavulanate and intravenous antimicrobials commonly used in pregnancy was high (Table 47.5). Susceptibilities of isolates collected specifically from patients in obstetrics/gynecology locations were similar to those for isolates from all women aged 16–45 years, with the exception that enterococcal isolates were 100% ampicillin-susceptible, and *E. coli* isolates were 100% susceptible to nitrofurantoin.

Because GFR is increased by 30–50% in pregnancy, doses of some drugs such as aminoglycosides and ceftriaxone must be adjusted accordingly;[75] for aminoglycosides, serum drug levels are helpful. Other agents, such as cefazolin, do not require dose adjustment. Nitrofurantoin should not be used in pyelonephritis, as it has limited parenchymal penetration.

Once afebrile, if oral intake is good and there is no diarrhea, treatment may be changed to oral antibiotics to complete a 10–14 day course.[76] A urine culture should be performed 1–2 weeks after treatment is completed. Women who do not improve within 48 hours of initial antibiotic treatment should be evaluated for possible obstruction or abscess.

Women who have had pyelonephritis or with recurrent UTI should receive preventive antibiotic treatment. Daily suppression with nitrofurantoin[73] or cephalexin, or a postcoital dose[70] until 4–6 weeks postpartum has been recommended. Evidence from randomized controlled trials support the efficacy of adjunctive measures such as increased intake of cranberry and blueberry products in prevention of UTI in women with recurrent infections.[77]

Pneumonia

Pneumonia occurs in up to 1% of pregnancies,[66] and is poorly tolerated due to increased oxygen requirements, and decreased buffering capacity with decreased ability to compensate for acidemia. Because of the greater affinity of fetal hemoglobin for oxygen, the fetus is relatively protected until maternal oxygen saturation becomes <90% (PaO_2 < 65 mmHg). Before antibiotics, mortality was 30% in pregnant women with pneumonia, and now is about 4%,[78] but remains the third most common cause of death in this group.[79] Mortality is highest in the third trimester. *Streptococcus pneumoniae* and varicella zoster are the most common causes of severe pneumonia in pregnancy.

Bacterial Pneumonia

With the exception of aspiration pneumonia in the third trimester, susceptibility to bacterial pneumonia does not appear to be increased by pregnancy itself. However, other medical conditions, particularly asthma and anemia, substantially increase the risk of bacterial pneumonia, and corticosteroid treatment for enhancement of fetal lung maturity appears to increase the risk of nosocomial pneumonia.[80] In community-acquired pneumonia, the most common bacterial pathogens are similar to those causing disease in non-pregnant adults, and include pneumococcus, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. However, up to 1 in 5 pregnant women admitted with bacterial pneumonia requires intensive care management,[81] and 10–20% require intubation and mechanical ventilation.[80] The frequency of complications such as bacteremia (16%) and empyema (8%) is also increased. Clinical symptoms are similar to those in

TABLE 47.5 Susceptibility of urinary tract isolates of *E. coli* to commonly used antibiotics

	Antimicrobial	Women aged 16–30 years	Women aged 31–45 years
Oral	Ampicillin	57%	46%
	Amoxicillin/clavulanate	93%	90%
	Cephalothin	74%	64%
	Nitrofurantoin	98%	94%
	Trimethoprim/ sulfamethoxazole	74%	64%
Solely parenteral agents	Aztreonam	99%	100%
	Cefazolin	93%	89%
	Cefotetan	99%	99%
	Ceftriaxone,ceftazidime, cefotaxime	>99%	>99%
	Gentamicin	95%	93%

non-pregnant women, and include fever, cough, pleuritic chest pain, rigors, and chills.

All pregnant women with a possible diagnosis of pneumonia should undergo chest radiography, and should be admitted at least initially for observation and intravenous antibiotics. The applicability of guidelines from the American Thoracic Society and British Thoracic Society for assessment of disease severity in pregnant women is unknown. Standard therapy for bacterial community-acquired pneumonia with ceftriaxone and azithromycin should be given. Vancomycin may be added in locales with decreased pneumococcal susceptibility to penicillin and ceftriaxone. Patients with suspected nosocomial pneumonia should be treated with intravenous antibiotics based on resistance patterns for local nosocomial isolates.

Viral Pneumonia

Viral pneumonia may be particularly severe in pregnancy. Varicella and influenza are the most frequent causes. Approximately 1 in 10 unvaccinated pregnant women will be susceptible to primary varicella. Varicella pneumonia usually occurs 3–5 days after onset of the rash, presenting with oral lesions, increased dyspnea, cough with blood-tinged respiratory secretions, and pleuritic chest pain. The risk of varicella pneumonia is increased in smokers, in women with underlying lung disease or immunosuppression, in women with more than 100 skin lesions, in women infected later in pregnancy, or when varicella has been acquired from a household contact.[82] Chest radiography demonstrates interstitial, nodular lesions with a ground-glass appearance, or local infiltrates, and should be performed in women who develop consistent symptoms. Although varicella pneumonia occurs at the same rate as in non-pregnant adults, disease is more severe and mortality rates may be 35–40%.[83,84] Maternal and fetal outcomes are improved by treatment with intravenous acyclovir 10 mg/kg every 8 hours. Mortality is highest when varicella pneumonia occurs in the third trimester.[82] When there is a known exposure, administration of Varicella Zoster Immune Globulin (VZIG) within 96 hours can prevent or attenuate infection. Varicella infection may also be transmitted to the fetus, and is discussed later in this chapter.

Illness due to influenza in pregnancy is increased 10-fold over non-pregnant women without other illnesses. The risk of influenza pneumonia is also increased in pregnancy.[85] In the 1918–1919 pandemic, the mortality rate for pregnant women with influenza pneumonia was 50%. Although the safety of amantidine and neuraminidase inhibitors is unknown in pregnancy, they should be given in severe illness. The influenza vaccine is considered safe for use in pregnancy, and immunization is recommended for prevention of illness due to influenza.

Although there is limited experience with infection due to SARS-coronavirus in pregnant women, the experience from the Hong Kong outbreak suggests a fatality rate of 25%. Half of the affected women received intensive care, and one-third required mechanical ventilation. More than half of the women in their first trimester had spontaneous fetal loss. Of the five women who presented after 24 weeks gestation, four delivered pre-term.[86]

Tuberculosis

Pregnancy-related tuberculosis has increased in the United States and other developed countries because of demographic changes, including an increase in immigrants with underlying infection, or at risk for acquisition of tuberculosis in immigrant communities.[87]

In contrast to older literature, recent studies do not show an increased risk in pregnant women of developing active tuberculosis,[87,88] and morbidity and mortality were not increased when pregnant women received appropriate antituberculosis treatment.[89] However, late diagnosis or incomplete treatment are associated with increased morbidity and mortality.[87] Treatment of tuberculosis is similar for pregnant and nonpregnant adults, with the exception that streptomycin, kanamycin, amikacin, capreomycin, and fluoroquinolones should not be used in pregnant women unless no other treatment options are available. Streptomycin has been clearly documented to cause congenital deafness. Pyridoxine (25 mg day) supplementation is required when isoniazid is given.[90]

Fungal Pneumonia

In the first two trimesters of pregnancy, *Coccidioides immitis* causes a mild influenza-like illness and pneumonia, but in the third trimester of pregnancy the risk for dissemination is increased.[91–93] Immunologic and hormonal changes during pregnancy and the postpartum period are thought responsible for increased frequency and severity of disease. Disseminated disease is associated with a very high mortality rate, and treatment with amphotericin B is recommended.

Puerperal Infections

Fever

In the puerperal period, spiking fever greater than 39 °C (102.2 °F) is usually caused by infection with bacteria, particularly *Streptococcus pyogenes* (group A beta-hemolytic streptococcus), the classic cause of childbed fever, or *Streptococcus agalactiae* (group B beta-hemolytic streptococcus). Infections with group A streptococci can be complicated by toxic shock syndrome.[94] Persistent low-grade fever also suggests bacterial infection.

Endometritis

Postpartum abdominal pain, tenderness, and fever, suggest the diagnosis of endometritis, an infection of the decidua,

myometrium, and surrounding tissues. Bacteremia with chills or rigors may occur. Other findings, such as foul-smelling lochia and leukocytosis, may be observed in women without endometritis and are not diagnostic. Most severe endometritis occurs 'early,' within the first 48 hours after delivery. 'Late'-onset endometritis can appear up to 6 weeks postpartum, but symptoms are generally milder.[95] For the most part, endometritis is an 'ascending' infection, caused by microorganisms colonizing the vagina such as the beta-hemolytic streptococci, other streptococci, enterococci, *S. aureus*, Gram-negative enteric bacteria such as *E. coli*, *Klebsiella*, and *Proteus* species, anaerobic organisms such as *Bacteroides, Prevotella*, *Fusobacterium*, and *Clostridium* species, and *Chlamydia trachomatis*, *Mycoplasma* species, *Ureaplasm urealyticum*, and *Neisseria gonorrhoeae.*

In the United States, endometritis is rare after vaginal delivery (1.3%), but the risk more than triples after interventions such as internal fetal monitoring, multiple cervical examinations, or after prolonged rupture of the membranes. Intrapartum chorioamnionitis raises the risk to 13%.[96] The duration of membrane rupture before delivery increases the risks of both chorioamnionitis and endometritis, which more than double after 12 hours and 16 hours, respectively.[97] Intrapartum chorioamnionitis can also occur preterm, or in women with intact membranes,[98] and organisms such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Listeria monocytogenes*, should also be considered.[99]

Cesarean delivery is the greatest risk factor for endometritis. Prior to widespread perioperative antibiotic prophylaxis, endometritis occurred in up to 50% of patients. Administration of a first- or second-generation cephalosporin intraoperatively after clamping of the umbilical cord decreases the rate to 12–17%.[100] Andrews and colleagues have reported that addition of intravenous azithromycin to cefotetan or cefoxitin prophylaxis further decreased the rate of pos-cesarean endometritis to about 2%, even in a high-risk population.[101] The benefit of azithromycin presumably relates to its activity against *Ureaplasma urealyticum* or mycoplasma, which have been associated with a three-fold increased risk of endometritis.

Endometritis occurs rarely after voluntary termination of pregnancy. When prophylactic antibiotics are administered, endometritis is a complication in about 0.5% of suction procedures, 1.5% of dilatation and curettage procedures, and 5% of uterine instillations. Reports of endometritis after medical abortion are very rare, and endometritis or genital tract infection have been reported in fewer than 0.013% of women treated with mifespristone.[102]

Reports linking toxic shock syndrome and infection with *Clostridium sordellii* and *Clostridium perfringens* after medical abortion[103,104] now appear to be linked to impairment of local innate immunity due to intravaginal use of the prostaglandin E2-pharmacomimetic misoprostol, but not to mifespristone.[105]

When endometritis is suspected, a pelvic examination should be performed and aerobic cultures obtained from the endocervical canal. Blood cultures may be positive in up to 20% of women.[99] In post-cesarean infections, initial treatment should include coverage for anaerobic organisms in addition to aerobic Gram-positive and Gram-negative bacteria, then modified based on culture results. Based on a meta-analysis of 39 clinical trials, the preferred regimen is clindamycin 900 mg plus gentamicin 1.5 mg/kg intravenously every 8 hours.[94] Clindamycin 2700 mg plus gentamicin 5 mg/kg intravenously as a single daily dose has been shown to be equally effective.[106] When fever persists after 48 hours, or enterococcal infection is suspected, addition of ampicillin 2 g intravenously every 6 hours or vancomycin is recommended.[107] Once the patient is afebrile, further treatment with oral antibiotics does not appear necessary. Persistence of fever and discomfort after 48 hours may signal the presence of a focus requiring debridement or drainage, such as pelvic abscess or an infected hematoma, or the presence of pelvic thrombophlebitis. Computerized tomography of the pelvis can be helpful in identifying these complications.

Wound Infections

The risk of wound infection following cesarean delivery ranges from 3% to 15%,[108] and is greatest in overweight and obese patients, after emergency cesarean delivery or membrane rupture more than 6 hours before delivery,[109] or if a subcutaneous hematoma develops.[108] The risk of wound infection increases more than nine-fold in women who are both obese and diabetic.[55] Intraoperative antimicrobial use to prevent endometritis concurrently decreases wound infections, to fewer than 2%.[100,101] Abscesses of the abdominal incision may form by the fourth postoperative day. Potential organisms include any that may have been present in the amniotic fluid at the time of delivery, methicillin-resistant staphylococci and nosocomial Gram-negative organisms.

Necrotizing fasciitis is a very rare complication of pregnancy, and in a large series of 5048 women undergoing cesarean section occurred in only nine.[110] All the infections were polymicrobial; no clear-cut risk factors could be identified. Necrotizing fasciitis can also occur at the site of an episiotomy or tear.

Cultures should be obtained from infected wounds, and necrotic tissue must be debrided. Abscesses should be drained and the pus sent for aerobic and anaerobic culture. Antibiotic management should include coverage for group A streptococci, methicillin-resistant *S. aureus* and Gram-negative organisms. Initial treatment of abscesses and necrotizing fasciitis also requires anti-anaerobic coverage. When an anaerobic infection is detected in a patient receiving clindamycin, an agent with broader anti-anaerobic coverage such as metronidazole or imipenem/cilastatin should be used.

Mastitis

Mastitis, or infection of the mammary glands, is common, and occurs in 5–33% of breast feeding women.[111] Almost all cases appear in the first 3 months, and very rarely at weaning. In a small percentage, mastitis is complicated by breast abscess or recurrent mastitis. Risk factors for mastitis include older maternal age, fatigue, employment outside the home, trauma to the skin or nipple, ineffective nursing technique, and milk stasis. The presenting symptoms are chills, rigors, and fever, in conjunction with unilateral breast tenderness, erythema, and decreased milk production. Most mastitis is caused by *S. aureus*, which may be transmitted to the mother from an infant nasally colonized before hospital discharge, followed by streptococci and *E. coli.* Prevention includes proper positioning of the infant and nursing technique. Initial treatment includes an antistaphylococcal oral antibiotic such as dicloxacillin or cephalothin, after cultures of expressed milk have been obtained. If fever persists, coverage should be modified for activity against methicillin-resistant *S. aureus.* Women should be treated for 10 days. If an abscess has formed it should be drained by ultrasound-guided needle aspiration, or surgically.

Prevention of Puerperal Infection

Prevention of puerperal infection includes strict adherence to Infection Control guidelines, particularly hand hygiene. In 1847, Semmelweiss described his experience in the maternity ward of the Vienna Hospital, which demonstrated that hand disinfection before examination of pregnant patients dramatically decreased mortality from childbed fever.[112] As the increased risk of endometritis associated with multiple exams and interventions such as fetal monitoring suggests, appropriate hand hygiene remains an essential measure to prevent nosocomial and iatrogenic infections.

Hepatitis E

Hepatitis E virus (HEV) is a nonenveloped, single-stranded RNA virus transmitted by the fecal–oral route that is a major cause of endemic hepatitis in Asia, the Middle East, Africa, and Central America. Like hepatitis A, HEV may cause fulminant hepatitis, encephalopathy, and death. However, in contrast to hepatitis A, B, or C, pregnancy is a major risk factor for severe infection due to hepatitis E virus in endemic areas. The increased rates of fulminant infection and death in pregnancy have been attributed to pregnancy-associated changes in immune function, and also to a direct effect of steroid hormones on viral regulatory elements controlling viral replication. In a study of Asian women with acute HEV, HEV viral load was more than 10-fold higher in pregnant than in non-pregnant women at similar stages of disease.[113] The severity of infection appears to be exacerbated by folate deficiency, which commonly complicates pregnancy in underdeveloped countries. Acute maternal infection in the second and third trimester is associated with pre-term birth, perinatal infant death, and acute neonatal infection with HEV, but infants who survive the initial period recover fully.[114,115]

Intestinal Parasitosis and Biliary Ascariasis

Infestation by intestinal parasites is common in pregnant women in the non-developed world. The extent of infection and types of infecting parasite vary according to region and socioeconomic conditions. A 2006 study in Venezuela found that 74% of women were affected by intestinal parasites, most commonly *Ascaris lumbricoides* (57%), *Trichuris trichuria* (36%), *Giardia lamblia* (14%), *Entamoeba histolytica* (12%), *Necator americanus* (8%), *Enterobius vermicularis* (6%), and *Strongyloides stercoralis* (3%). Pregnant women with intestinal parasites are more likely to be anemic,[116] but anemia may be the consequence of other confounding conditions rather than the parasite load. In most cases, pregnancy is not otherwise known to alter the course of the parasitic infection. An exception is infection with *A. lumbricoides*, which in pregnancy is more likely to cause biliary ascariasis. Biliary ascariasis may present as acute cholecystitis, cholangitis, biliary cholic, acute pancreatitis or hepatic abscess. Conservative treatment with bowel rest, antispasmodics, and antibiotics is successful in 68–80% cases, but the presence of dead worms, stones or strictures may prevent migration of the worms back to the duodenum, necessitating surgery. Animal models suggest the increased susceptibility to biliary ascariasis in pregnancy is due to relaxation of the sphincter of Oddi and decreased intestinal motility due to smooth muscle dysfunction as a consequence of increased progesterone and estrogen, particularly in the second and third trimesters.[117]

Malaria

Malarial infection causes increased maternal and perinatal infant morbidity and mortality, and it is associated with maternal anemia, low birthweight, and preterm birth. In high transmission areas, most women have partial protection due to previous infections, and severe maternal anemia and low birthweight babies are the primary complications. In low transmission areas, particularly in Asia and Latin American, women are less likely to have preexisting immunity, infections are more likely to be severe, and the risk of fatal infection is higher.[118]

Severe malaria in pregnancy is caused by *Plasmodium falciparum*. During pregnancy, even women from endemic areas who would be expected to have developed some clinical immunity to malaria can develop high parasitemias. Some evidence suggests that changes in maternal spleen function decrease parasite clearance and increase maternal susceptibility even within the first 8 weeks. However, the

major factor influencing the severity of malaria in pregnancy is the sequestration of parasitized erythrocytes by the placenta.

By the 10th to the 12th week of pregnancy, the placenta expresses chondroitin sulfate A (CSA), and can support the clonal expansion of a subpopulation of parasites that express an antigen able to bind to CSA.[119] The placenta can sequester a large number of parasitized erythrocytes, including late trophozoite and schizont stages that are not seen in the peripheral blood. Sequestration occurs throughout the intervillous space of the placenta, and is not limited to the vascular wall.[120] Binding to other antigens may occur, but appears to be less important. The parasitized cells can also circulate, but the detectable parasitemia underestimates the placental parasite load, and examination of peripheral blood can be falsely negative. The risk associated with malaria in pregnancy is greatest during the first pregnancy. After several pregnancies, the mother develops specific 'anti-adhesion' antibodies directed against the malarial antigens expressed by placental variants.[121,122]

In placental malaria, the intervillous spaces contain parasitized erythrocytes, and increased numbers of monocytes and macrophages (Figure 47.1). These phagocytic cells often contain hemozin pigment, which may also be present as free pigment or in fibrin deposits, and may also contain ingested parasitized erythrocytes (erythrophagocytosis) (Figure 47.2). The pigment deposits persist after the parasites have been cleared. The presence of both parasitized erythrocytes and hemozoin pigment indicate a chronic infection. When placental monocytes and macrophages are increased, changes in the placental cytokine balance are thought to contribute to poor outcome.[120] Malaria parasites

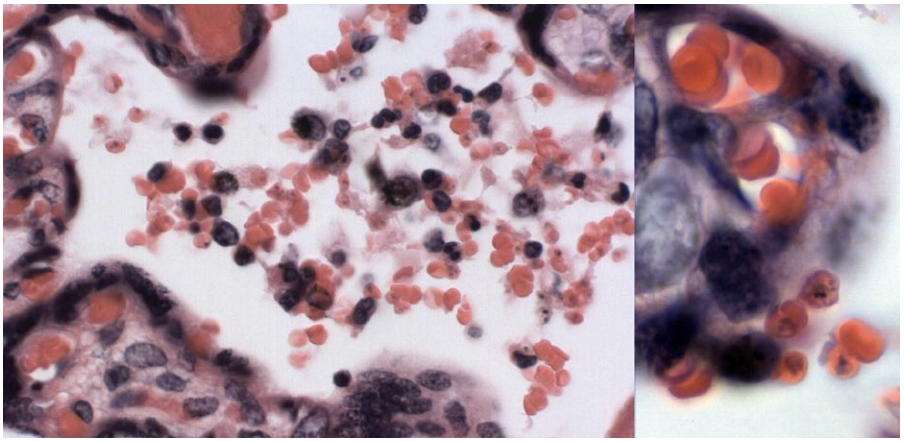

FIGURE 47.1 Placental malaria, H&E. *Left:* Sequestration of *P. falciparum*-infected erythrocytes in the intervillous space (maternal blood), and infiltration by monocytes and macrophages. The monocytic cells release proinflammatory cytokines including IFN-γ and IL-2. *Right:* There are multiple infected maternal erythrocytes in the intervillous space. By contrast, the fetal erythrocytes within the capillaries of the villous are not infected.

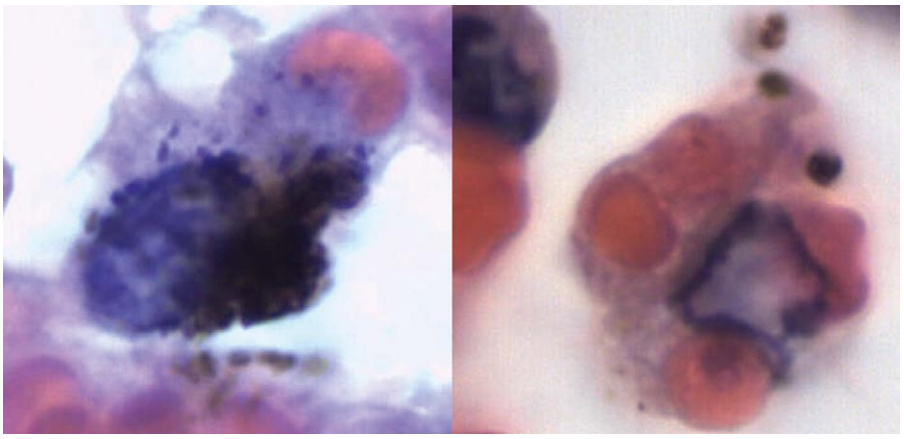

FIGURE 47.2 Placental malaria, H&E. *Left and right*: placental macrophages containing phagocytosed parasitized erythrocytes and brown hemozoin pigment. Some immune functions, such as production of chemokines and differentiation to dendritic cells, are impaired in cells containing large amounts of hemozoin pigment.

do not cross the placenta to infect the fetus, although leakage of maternal cells into the fetal circulation at parturition could potentially lead to infection of the infant. Other plasmodium species do not adhere to placental receptors, and infection does not have the same clinical impact, although chronic infection with *P. vivax* is associated with maternal anemia, and low birthweight.

Other factors that may increase susceptibility to malaria in pregnancy include sustained increases in cortisol and prolactin levels,[123] and HIV infection. HIV infection decreases the response to the variant-specific antigens responsible for binding to CSA, decreases the lymphoproliferative responses to malarial antigens, and impairs the cytokine response. In non-pregnant adults, the level of parasitemia is inversely correlated with the CD4 count.[124]

In malaria endemic areas, preventive measures include insecticide-treated nets to prevent mosquito bites, and intermittent preventive therapy in pregnancy. Intermittent treatment with at least two doses of sulfadoxine-pyramethamine in the second and third trimesters is recommended by the WHO. Women with HIV infection may require additional doses. Use of chloroquine for prophylaxis is no longer recommended due to resistance.[125]

Currently, the only antimalarials known to be safe for treatment during the first trimester of pregnancy are quinine, proguanil, chloroquine, and clindamycin. Artemisinin-based combination therapies (ACTs) are not recommended in the first trimester unless no other alternative is available. Recommendations for malaria treatment in pregnancy are available from the CDC and the WHO (summarized in Table 47.6).

Schistosomiasis

Schistosomiasis is a common parasitic infection in the developing world, and affects about 40 million women of childbearing age, mostly in sub-Saharan Africa (*S. haematobium* and *S. mansonii*) and the western Pacific (*S. japonicum*). In contrast to infection with malaria, pregnancy-related changes in immunity or parasite-specific antigen expression do not seem to be factors in the course of disease. However, schistosomiasis can adversely affect

TABLE 47.6 Recommendations for malaria treatment in pregnancy

Uncomplicated falciparum malaria

- First trimester
  Chloroquine-susceptible:
  Chloroquine phosphate, 600 mg base (=1000 mg salt) orally, followed by 300 mg base orally at 6, 24, and 48 hours for a total dose of 1500 mg base
  Hydroxychloroquine, 620 mg base (=800 mg salt) orally, followed by 310 mg base orally at 6, 24, and 48 hours for a total dose of 1550 mg base
  Chloroquine-resistant:
  Quinine 10 mg/kg plus clindamycin 5 mg/kg three times per day, × 7 days
  Artesunate 2 mg/kg per day plus clindamycin 5 mg/kg three times per day, × 7 days
- Second or third trimester
  Artesunate 2 mg/kg per day plus clindamycin 5 mg/kg three times per day, × 7 days
  Quinine 10 mg/kg plus clindamycin 5 mg/kg three times per day, × 7 days

Severe malaria

- Quinidine gluconate 6.25 mg base loading dose over 1–2 hours followed by 0.0125 mg base/kg continuous infusion, *plus* clindamycin for at least 24 hours, and until parasitemia is <1%. Treatment may be completed with oral quinine plus clindamycin. Treat patients for 3 days if disease was acquired in Africa or South America, and for 7 days if acquired in South-East Asia
- Artesunate 2 mg/kg per day plus clindamycin 5 mg/kg three times per day, × 7 days

Other antimalarial agents

- Artemisinin combination treatments (ACTs) , such as arthemether–lumefantrine, artesunate–amodiaquine, artesunate–mefloquine, and artesunate–sulfadoxine-pyramethamine, have been used extensively outside the United States, but should be avoided during the first trimester
- Atovaquone-proguanil tablets, 250 mg atovaquone/100 mg proguanil each, × 4 tablets orally per day × 3 days

pregnancy outcome, such as low birthweight (*japonicum*) and preterm delivery (*haematobium*). Potential pathogenic mechanisms include maternal iron deficiency anemia due to direct blood loss in the stool (*mansonii*, *japonicum*) or urine (*haematobium*), or associated with chronic disease, and inflammation in response to placental infection by immature worms and eggs with consequent cytokine production. In *S. haematobium* infection, stimulation of cytokine production following binding of circulating antigen to placental TLRs has been proposed. Similar outcomes can be shown in animal models. After experimental infection of rats with *S. mansonii*; infected rats have fewer pregnancies, fewer surviving pups, higher maternal death rates, higher spontaneous abortion rates, and lower pup weights at birth and in early infancy. Analogous findings are obtained after infection in pigs, and congenital transmission has also been described.[126]

The WHO considers pregnant women with schistosomiasis to be high-risk, and recommends treatment. If treated early in the disease course, hepatic, gastrointestinal, and urinary tract pathology is reversible. Praziquantel is listed as a pregnancy class B agent, but no adverse effects have been reported in 20 years of post-market monitoring.

INFECTIONS IN WHICH FETAL TRANSMISSION OR OTHER FETAL MORBIDITY IS THE PRIMARY CONCERN

For some infections during pregnancy, the mother is minimally, if at all, affected, but transmission to the fetus is a major concern, and the consequences of fetal infection can be devastating. In many infections, growth of the fetus may be affected (intra-uterine growth retardation) or the infant may be delivered prematurely (miscarriage or preterm birth), even in the absence of congenital infection.

'Torch' Agents

Toxoplasmosis

Toxoplasmosis is a zoonotic parasitic infection caused by infection with *Toxoplasma gondii.* Cats are the definitive hosts for this parasite; humans are intermediate hosts and are infected by cat exposure, or by ingestion of raw or undercooked meat, infected water, or contaminated soil.[127] Cats are less likely to be infected in Asia, and the risk from direct cat exposure is less likely than in the United States and Europe.[128] Congenital toxoplasmosis usually occurs in association with primary infection during pregnancy, although congenital transmission has been reported from chronically infected mothers, even in the absence of immunocompromise.[129,130] *T. gondii* actively invades cells, and can cross biological barriers, including the placenta and blood–brain barrier. Congenital toxoplasmosis causes a disseminated infection in the fetus, and *T. gondii* DNA can be detected in amniotic fluid, blood, cerebrospinal fluid, and other fetal tissues.

The incubation period of toxoplasmosis is 4 to 21 days. Most cases are asymptomatic in the mother, or present only with localized lymphadenopathy or symptoms of mononucleosis. An evaluation for possible congenital toxoplasmosis includes maternal serology, and molecular amplification testing for *T. gondii* DNA from amniotic fluid. Maternal IgM antibody appears within 1–2 weeks after infection, followed by IgA and IgE. The IgM response peaks at 2 months, and generally wanes after 6–9 months; the IgG response peaks after 4 months. Some authors suggest that in pregnant seroconverters, testing IgA and IgE levels, and the binding avidity of IgG, IgA, and IgE may be helpful, since avidity increases during infection, and low avidity suggests a more recent infection.

Congenital infection should be treated before birth, with the best outcomes reported if treatment is initiated within 4 weeks of seroconversion. Treatment should include sulfadiazine plus pyramethamine until birth; clindamycin should be used in early pregnancy.

The risk of primary toxoplasmosis in pregnancy can be minimized by avoiding consumption of raw or undercooked meat, washing hands and utensils thoroughly after contact with raw meat, washing all uncooked vegetables, wearing gloves when in contact with soil, and washing hands thoroughly immediately thereafter. Cats should be kept indoors. Pregnant women should not change cat litter, and should wash their hands immediately after contact with cats.

Rubella

Rubella (German measles) is a generally mild childhood illness that causes devastating congenital infection in infants of non-immune mothers, particularly when infection is acquired in the first trimester. After the availability of vaccine in 1969, the number of rubella cases declined in the United States, and by 1979, the characteristic 6- to 9-year epidemic cycle of rubella was no longer evident. Congenital transmission has been eliminated in the United States since 2005, and substantial progress towards elimination in the Western Hemisphere and worldwide has been made due to aggressive vaccination programs.[131]

Rubella virus is transmitted by respiratory tract aerosols, and enters the susceptible host through the nasopharyngeal epithelium. The virus is transported via the blood to the lymph nodes and spleen, and replicates in reticuloendothelial cells. Six to 20 days after the initial infection, the virus reenters the blood and disseminates widely, and the rash appears shortly thereafter. Virus is shed from the nasopharynx beginning 3–8 days after exposure, and for 6–14 days after onset of the rash, accounting for an extended period of infectivity. In most younger children,

rubella is a mild illness, causing a low-grade fever that lasts for less than 24 hours, a maculopapular rash over the face and neck that lasts 2 or 3 days, and malaise. Many children are completely asymptomatic, although rare cases of rubella encephalitis have been reported. In older children, adolescents, and adults, rubella symptoms may include several days of fever, headache, malaise, coryza and conjunctivitis. Illness may be complicated by cervical adenopathy, which can precede the rash by several days, and by arthralgia or arthritis, which occurs in up to 70% of older girls and women. Thrombocytopenic purpura may also occur rarely.

During pregnancy, rubella infection is transmitted transplacentally, and can cause a disseminated infection, resulting in miscarriage, stillbirth or damage to various fetal organs (the congenital rubella syndrome). Rubella infection causes cell death, inhibition of mitosis, and vascular endothelial damage, and its impact is greatest during organogenesis. When infection occurs during the first trimester of pregnancy, 50–90% of fetuses will be affected, but the percentage of affected infants declines progressively during the second trimester.[132] The classic findings in congenital rubella include cataracts/congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, and pigmentary retinopathy, but all organ systems can be affected. Congenital rubella infection also causes encephalitis, mental retardation, pneumonia, hepatitis, thrombocytopenia, growth plate defects, diabetes mellitus, and thyroiditis.[133] Congenitally infected babies excrete rubella virus at birth and for months, and are highly infectious.

Rubella is a vaccine-preventable illness, and live attenuated rubella virus vaccines have been available and in use for over 40 years. Currently, two doses of combined measles–mumps–rubella (MMR) vaccine are recommended in the current schedule for children and adolescents. Susceptible women of childbearing age should be vaccinated. Although extensive postvaccination surveillance has not turned up any instance of congenital rubella following inadvertent vaccine administration to pregnant women, current recommendations are that women known to be pregnant should not be vaccinated, and conception should be avoided for 28 days after receipt of a rubella-containing vaccine. Adult women can develop acute transient arthralgia and arthritis after vaccination, but evidence does not support an association with chronic joint problems. Subclinical thrombocytopenia may be observed after vaccination.

Cytomegalovirus

Infection with human cytomegalovirus (HCMV or HHV-5) is a common congenital viral infection, affecting at least 1% of live-born infants in developed countries. Most severe fetal infections occur during primary maternal infection, with a congenital transmission rate of about 40%. Of these infants, 10–15% will be symptomatic at birth and an additional 5–10% will develop late neurologic findings.[134] Primary CMV infection during the third trimester has the highest rate of congenital transmission. In early pregnancy, spontaneous abortion can occur, often accompanied by evidence of placental infection, even without signs of fetal infection. Congenital infection can also follow reactivation of endogenous maternal CMV infection, or if the mother is reinfected with a new strain, but at a lower rate, presumably because of partial maternal immunity.[135] The risk of congenital infection in non-primary infection had previously been estimated at about 1%,[135] but a recent prospective study found a much higher rate of almost 20%.[134] It is now recognized that over 60% of congenitally infected infants have mothers with previous immunity to CMV, but with evidence of secondary infection during pregnancy. Most of these infants are asymptomatic at birth but are at risk for late neurologic disease.[136]

HCMV infects many cell types, including fibroblasts, epithelial and endothelial cells, macrophages, and muscle cells, and latency is established once the primary infection is controlled. The consequence is that congenital HCMV may cause symptoms in virtually any organ system, most commonly the central nervous system, liver, spleen, gastrointestinal tract, and hematopoietic system. Disease may be mild or fulminant, with infant mortality rates of 25%. Findings typical of congenital HCMV infection include intra-uterine growth retardation, jaundice, hepatosplenomegaly, enteritis, pneumonitis with respiratory distress, rash, chorioretinitis, pancytopenia., and central nervous system findings such as meningoencephalitis, calcifications, microcephaly, ventriculomegaly, ocular abnormalities, and cerebellar hypoplasia. Related symptoms include lethargy, seizures, and cognitive and motor deficits. Hearing loss affects 50–60% of infants with other findings of HCMV at birth, and 10–15% of infants who appear asymptomatic. Other deficits such as mental retardation, and visual and motor impairment are less common in infants who are asymptomatic at birth.[136,137]

In primary maternal HCMV infection, maternal viremia leads to placental infection, and subsequent hematogenous dissemination to the fetus. Maternal leukocytes transmit infection, either by migration later in pregnancy and direct contact with fetal endothelium, or indirectly by contact with uterine endothelial cells, which are in contact with cells of the cytotrophoblast. In cases of congenital transmission from mothers with recurrent CMV, local immunosuppression in the uterus is thought to allow HCMV reactivation in uterine macrophages, which then infect invading cytotrophoblast cells, allowing viral spread to the fetus. In an infected fetus, HCMV can be detected in blood, and viremia persists for months after birth.

Congenital HCMV should be considered in mothers who develop primary or secondary CMV infection. Primary maternal HCMV infection is documented by positive

viral culture, or by molecular testing. Seroconversion is suggestive, but IgM antibodies can remain positive for up to 18 months, thus may not reflect acute infection. Secondary infection is suggested by a significant increase in IgG titer, or by the presence of IgM. Because IgM assays can give false-positive results, routine serologic screening has not been recommended during pregnancy in the absence of maternal symptoms or findings on ultrasonography.

In a newborn infant, a diagnosis of congenital infection can be made by detecting the virus in sputum or urine. Large amounts of virus are shed and culture is nearly 100% sensitive and specific in this setting. Molecular methods are not needed. However, antenatal diagnosis can be more difficult. Fetal blood sampling for CMV-specific IgM antibody is no longer recommended because of risks associated with cordocentesis, and because specific anti-CMV IgM may not develop until late in pregnancy. Assays of amniotic fluid for virus are preferred. In amniotic fluid, detection of HCMV by conventional or shell vial culture methods has been the gold standard for prenatal diagnosis, but molecular detection is more sensitive (90% vs. 80% by amniotic fluid culture) and is still highly specific. Detection of even small amounts of HCMV DNA correlates with congenital infection at birth. The importance of quantitative HCMV DNA testing is less clear, since levels do not correlate with structural abnormalities on ultrasound or with symptomatic versus asymptomatic infection at birth in all studies.[135]

When amniotic fluid is tested by virus culture, and assays for viral DNA, Immediate-Early mRNA, and pp67 (late expression) mRNA, obtaining positive results in two or more assays has a positive predictive value of 96.7–100% for congenital infection. Conversely, inability to detect HCMV in two or more assays has a negative predictive value of 84–93%.

Unfortunately, antenatal testing procedures are limited by the risk of false-negative results when performed too early. The sensitivity of prenatal diagnosis increases from 50% to 76.2% and 91.3%, when <8, 9–12 and >13 weeks, respectively, elapse between the maternal infection and testing.[135] At least 5–7 weeks are required after fetal infection for viral dissemination, followed by viral replication in the kidney and excretion of virus into the amniotic fluid via the fetal urine. Thus testing is not considered reliable before the 21st week of gestation, or less than 6 weeks after maternal infection. Contamination with maternal blood or tissue can also occur, leading to false-positive results.[136] Because of these limitations, recommendations have been to limit prenatal diagnosis only to those mothers with known or highly suspected primary HCMV infection and/or in the presence of fetal ultrasonographic abnormalities.

There is no FDA-approved antiviral agent for treatment of congenital CMV infection. Treatment of symptomatic infants diagnosed at birth with intravenous ganciclovir 6 mg/kg every 12 hours for 6 weeks benefited infants with pneumonia and prevented hearing loss.[138] The efficacy of antenatal ganciclovir for prevention of sequelae due to congenital HCMV infection has not been conclusively demonstrated. In a prospective clinical trial performed in Italy, treatment of pregnant women with confirmed primary CMV with CMV-specific immune globulin decreased the rate of symptomatic congenital infection at birth to 3%, in contrast to 50% in the untreated group.[137]

HCMV may also be transmitted after birth via breast milk. Postnatally acquired HCMV does not appear to be associated with neurologic or cognitive abnormalities, or other increased morbidity, except in cases of coincident congenital HIV infection.[136]

Most transmission of HCMV occurs by contact with blood or body secretions such as saliva, urine, feces, semen, vaginal secretions, breast milk or tears from an infected person. Risk reduction includes limiting potential exposure by practicing monogamy, avoiding contact with saliva and urine, particularly of toddlers and very young children, and following handwashing and general good hygiene practices.

Herpes Simplex Virus (HSV)

HSV infection is more severe in pregnancy. Recurrences are more frequent, more severe, and last longer, and primary infection may lead to severe illness with a maternal mortality rate of about 50% if disseminated infection occurs.[139] Because seropositivity is high in the general population, only a small number of women have a true primary HSV infection during pregnancy. Severe primary disease is most likely in women who develop gingivostomatitis or vulvovaginitis, particularly when infection occurs in the third trimester,[140] and is associated with disseminated skin lesions and evidence of multiorgan involvement including hepatitis and encephalitis.

Maternal HSV infection is also associated with congenital infection, which affects 1 in 3200 to 1 in 5000 newborns. Maternal antibody is protective, and influences the rate of transmission, which decreases from 50% for primary maternal infection, to 33% for a non-primary first episode (infection with HSV-1 or HSV-2 in a woman with serologic evidence of previous infection with the other type), to 3% for recurrent HSV infection.

Intra-uterine infection accounts for only 5% of congenital HSV infections. The greatest risk of intra-uterine HSV transmission occurs with primary disseminated maternal infection in the first 20 weeks of pregnancy, but intrauterine infections have also been reported in association with recurrent maternal infection during that period.[141] Intra-uterine infection may be a consequence either of viremia or ascending infection. Most intra-uterine infections are caused by HSV-2. Several factors may be contributory, including a greater background seropositivity to HSV-1, smaller likelihood of recurrent infection due to HSV-1, and greater resistance to HSV-1 infection by placental syncytiotrophoblast cells which lack receptors for HSV-1 entry. As

with other intra-uterine infections, risks include pregnancy loss and congenital malformations. Classically, infants with intra-uterine HSV infection develop severe skin (vesicles, scarring), eye (microphthalmia, chorioretinitis, cataracts), and brain (microcephaly, hydrocephaly, intracranial calcifications, encepahlomalacia, seizures) lesions. Limb hypoplasia similar to that seen in congenital varicella syndrome has also been reported.

Transmission at the time of delivery accounts for the majority (90%) of congenital HSV infections. Because the infant is most commonly infected with HSV by contact with maternal lesions during passage through the birth canal, transmission can be avoided by treatment of women with recurrent HSV with acyclovir at term, and by cesarean delivery if lesions are present. Cesarean delivery reduces the risk of neonatal HSV by 85%. Although lesions are almost always very painful during primary infection, symptoms are usually less severe in recurrent infections. Some patients may even be asymptomatic, particularly if lesions are limited to the cervix and vagina. Thus, careful examination of the external genitalia and the cervix must be performed when the mother enters labor. Neonates may have infection only of the skin, eyes, mouth, or more serious CNS or disseminated infection, which are associated with infant mortality (15% and 57%, respectively) and residual neurologic impairment.

Type-specific serologic testing early in pregnancy is useful to determine susceptibility to infection, risk for recurrence (greater for HSV-2 infections), and to help distinguish primary vs. recurrent infection and the associated risk of congenital transmission for women who become symptomatic later in pregnancy. In primary or recurrent infection, the diagnosis can be confirmed rapidly by direct fluorescent antibody testing, or shell vial and conventional viral culture of material from maternal lesions. Molecular methods such as PCR for HSV DNA are generally not required when lesions are present.

HSV infections in pregnant women should be treated in the same way as in nonpregnant women, with the caveat that of antiviral agents, acyclovir has been used most often and does not appear to be associated with any teratogenic effects. Regimens include acyclovir 400 mg orally three times per day or acyclovir 200 mg orally 5 times per day for 7–10 days (primary infections) or 5 days (recurrent infections). Suppression of HSV recurrences with acyclovir 400 mg orally three times per day, beginning in the 36th week of pregnancy has been shown to reduce both recurrences around the time of delivery, and the need for cesarean section.[142] Valacyclovir also appears safe in pregnancy, but has been used less extensively.

The best measure to reduce congenital HSV infection is prevention of transmission to the mother. Steps to prevent a primary infection in the mother or infection with a new HSV strain from an HSV-infected contact include minimizing exposure by avoiding intercourse during outbreaks, the use of condoms, avoidance of oro-labial contact, and by antiviral treatment for the HSV-infected partner.

Parvovirus

Parvovirus B19 causes the childhood illness erythema infectiosum (fifth disease). In adults, particularly women, infection can be associated with acute and sometimes persistent symmetrical arthritis of the wrists, ankles, and knees. Patients with underlying diseases may develop more severe symptoms, such as transient aplastic crisis in patients with sickle cell anemia, or refractory anemia and thrombocytopenia in immunocompromised individuals. Infection during the second trimester of pregnancy can cause fetal anemia, hydrops, and death, even when maternal infection is mild or asymptomatic.

Immunity to parvovirus is based primarily on neutralizing antibody, and pregnancy does not appear to affect susceptibility to infection or the course of the disease in the mother. Data from the United States and Europe indicate that up to one half of women are susceptible at the time of pregnancy, and 1.5% (in endemic periods) to 13% (during epidemics) of previously seronegative women of childbearing age are infected with parvovirus annually.[143]

Viremia develops 4–14 days after exposure to parvovirus, and may produce symptoms of headache, fever, malaise, and coryza, or may be asymptomatic in up to 50% of individuals. Infection of bone marrow erythrocyte progenitor cells (the precursors of erythroblasts and megakaryocytes) causes formation of giant pronormoblasts, cytoplasmic vacuoles, and large eosinophilic nuclear inclusion bodies, followed by cell death and an acute drop in peripheral reticulocytes, causing anemia. Leukopenia and thrombocytopenia may also occur. The pathogenic effects of infection in other cells, such as mature erythrocytes, synovium, placenta, fetal myocardium and endothelium, are less clear.

Transmission to the fetus occurs in about one-third of maternal infections. When infection occurs between weeks 11 and 23, during the period of hepatic hematopoiesis, the fetus can develop severe fetal anemia, leading to high output cardiac failure and non-immune hydrops because of the short lifespan of fetal erythrocytes, and the three- to fourfold increase in erythrocytes needed to accommodate fetal growth during this period. Estimates from retrospective case series place the overall risk of fetal hydrops following parvovirus infection from 1% to 4%, and as much as 7% when infection occurs between 13 and 20 weeks gestational age. Death from hydrops occurs in 50–90% of untreated cases within 2–4 weeks after maternal infection.[144] Treatment includes intra-uterine transfusion, which improves survival to 85% in the cases of severe hydrops.[145,146] Early studies suggested that the overall outcome after maternal parvovirus infection is good for liveborn infants,[147] and growth and general health are normal.[148] However, in a recent

follow-up study of 24 infants treated with transfusions for hydrops, 3 of the 16 surviving children (32%) had developmental delays not attributable to other etiologies.[149]

Parvovirus binds to susceptible cells through globoside or P-antigen, and individuals lacking P-antigens cannot be infected by the virus. However, P-antigen expression is not sufficient for viral entry into the cell, which requires the presence of a functional co-receptor such as the $\alpha5\beta1$ integrin,[150] or possibly Ku80.[151] Placental expression of P-antigen, which is highest early in pregnancy and gradually declines to become undetectable in the third trimester, may influence the likelihood of maternal–fetal transmission. A virally encoded phosphoprotein, NS1, controls viral transcription and replication, and causes host cell death, both by direct toxicity and by promoting cell cycle arrest and apoptosis. The NS1 protein also causes release of placental proinflammatory cytokines that are associated with a poor pregnancy outcome.

In immunocompetent subjects, virus-specific IgM appears within 4 days of symptoms, or 21–24 days after exposure, and controls viremia. Specific IgG appears within 7–10 days and is associated with immune complex formation, the development of arthropathy, and the characteristic lacy, red 'slapped cheek' rash, and the recovery of reticulocytes and resolution of anemia. Diagnosis of maternal parvovirus infection is primarily based on serology. Virus-specific IgM persists from 2 up to 6 months; commercially available assays are sensitive and specific. Molecular methods, such as real-time PCR for parvovirus B19 DNA, or in situ hybridization, should be used to evaluate fetal but not maternal specimens, since viral DNA can persist in asymptomatic individuals.[152] Parvovirus B19 cannot be cultured by routine methods.

Once maternal infection has been diagnosed, the fetus should be monitored weekly by ultrasonography for 14–16 weeks for increased peak systolic flow velocity of the middle cerebral artery, which is a sensitive marker for fetal anemia. Development of hydrops is manifested by combinations of generalized edema, subcutaneous edema, ascites, pleural effusion, pericardial effusion, placental edema, and polyhydramnios. The optimal stage for intervention by fetal transfusion has not been established.

Recently, third trimester fetal loss in the absence of fetal hydrops, but associated with parvovirus B19 DNA in placental tissues has been reported. Fetal loss occurred most often at 4–6 weeks, but could occur up to 12 weeks, after infection. In these cases, maternal infection was asymptomatic, and serologic response was delayed or absent. The cause of death in these infants was not clear at autopsy.

Most parvovirus infections occur in the winter and spring, with epidemics at 3–5 year intervals. Respiratory secretions from an infected person are very contagious. In the immunocompetent, secretions are only infectious before appearance of the rash or arthropathy, but immunocompromised individuals unable to make antibody cannot clear the virus and are infectious for an extended period. Hand and respiratory hygiene are recommended for prevention. Except in healthcare settings, isolation or restriction of activities has not been recommended by the CDC, since a diagnosis is usually made once the characteristic rash has appeared, and the individual is no longer infectious. Most pregnant women acquire infection in a family setting. Because parvovirus B19 is a small, non-enveloped single-stranded DNA virus, it is stable to current blood decontamination methods, and can also be transmitted through contaminated blood products. A recombinant vaccine (Medimmune) to VP1 and VP2 capsid proteins is under evaluation. The benefit of intravenous immunoglobulin for prophylaxis after exposure has not been systematically evaluated.

Other recently described members of the Parvoviridae found in human specimens include three Erythrovirus strains (A6, K71 and V9) which are closely related to B19, two novel parvoviruses, PARV4 and PARV5, and human bocavirus. Only limited information is available about the role of these strains in clinical disease.

Varicella Zoster

As described earlier in this chapter, chickenpox (varicella zoster virus, VZV) during pregnancy can be associated with a more severe course of disease, and varicella pneumonia presents a risk for maternal ventilatory failure and associated high mortality. There is also a risk to the developing fetus, usually as a consequence of maternal viremia. When infection occurs during the first 24 weeks of pregnancy, congenital varicella will develop in almost 2%, manifested by dermatomal skin lesions (cicatricial scars, skin loss), low birthweight, eye (microphthalmia, enophthalmia, chorioretinitis, cataracts, nystagmus, anisocoria, optic atrophy) and brain lesions (cortical atrophy, spinal cord atrophy, limb paresis, microcephaly, seizures, Horner's syndrome, encephalitis, dysphagia), and skeletal anomalies such as limb hypoplasia. Almost one-third of infants with congenital varicella die within a few months. The fetus is unable to mount a cell-mediated immune-response to VZV infection, and zoster-like reactivations with associated encephalitis are thought to cause the typical lesions of congenital varicella.

Neonatal varicella occurs in infants whose mothers are infected in the 3 weeks prior to delivery. Infants infected 2–3 weeks prior to delivery develop chickenpox, but generally do well since some maternal IgG will have developed and been transferred to the infant. Infants of mothers infected closer to delivery (maternal rash in the 5 days prior to delivery or just after) will not have acquired maternal antibody. These infants have 17–30% chance of developing fulminant disseminated infection, with a 20% risk of death.[153] Infections with VZV occur due to transplacental infection following maternal viremia, ascending infection during birth, or respiratory infection after birth. Maternal shingles

does not appear to be associated with risk of congenital infection, and maternal antibodies appear to be protective.

The diagnosis of maternal varicella can generally be made clinically, and confirmed rapidly by direct fluorescent antibody testing, or shell vial and conventional viral culture of material from maternal lesions.

Serology and culture are less reliable in congenital varicella, and molecular methods such as PCR for viral DNA may be needed for differentiation from HSV-2 or coxsackie B virus, which may present similarly. Amniotic fluid can be tested antenatally, but should be limited to cases in which fetal ultrasound examination demonstrates findings consistent with the diagnosis, since a positive amniotic fluid result may be obtained in the absence of fetal malformations.

Active immunization of women before pregnancy is recommended. Since the varicella vaccine contains a live, although attenuated, virus, women should wait at least 4 weeks after vaccination before becoming pregnant, and vaccine should not be given to women who are already pregnant. Exposed, susceptible pregnant women should receive Varicella Zoster Immune Globulin (VZIG) 125 U/10 kg (maximum 625 U) intramuscularly within 72–96 hours.

Little information is available about the use of acyclovir for prophylaxis after maternal exposure or for prevention of congenital varicella syndrome, but may be of benefit. Higher doses of acyclovir (800 mg orally five times per day) are required. Timing also appears to be an issue, and treatment on the 7th day after exposure is recommended.[82]

Classical Sexually Transmitted Infections (STIs)

Many women continue to have intercourse even late in pregnancy, and thus are at continued risk of acquiring an STI. Data from the CDC indicate that more than 15% of new STIs in women of child-bearing age occur during pregnancy. STIs are discussed elsewhere in this volume, and this discussion focuses primarily on the impact of STIs on pregnancy and congenital infection. Screening and treatment guidelines have been established by the CDC[154] and by the American College of Obstetricians and Gynecologists.[155]

Chlamydia

Infection with *Chlamydia trachomatis* (CT) may be the most commonly diagnosed bacterial STI in pregnancy. CT is a frequent cause of cervicitis, endometritis, salpingitis, peritonitis, reactive arthritis, Reiter syndrome, and infertility associated with pelvic infection. Most epidemiologic data suggests that women with previous pelvic infections, whether symptomatic or asymptomatic, are at risk for ectopic pregnancy. CT is transmitted to the infant during passage through the birth canal in 30–50% of infected women. In neonates, CT causes conjunctivitis, pharyngitis, pneumonia, and genital tract infection. CT conjunctivitis is not prevented by neonatal prophylaxis and requires prolonged treatment to prevent blindness.

All pregnant women should be tested at the first prenatal visit. If positive, they should be treated and retested 3 weeks later. All women less than 25 years or at increased risk (new partners, multiple partners, previous STD, or in areas with a high prevalence) should be retested in the third trimester.

Women should be screened using nucleic acid amplification tests for urine, vaginal, and cervical specimens. Direct fluorescent antibody tests or culture are recommended for rectal specimens, although nucleic acid amplification tests are more sensitive and have been validated in some laboratories. Treatment with azithromycin 1 g orally as a single dose is preferred. Doxycycline should not be administered in pregnancy.

Gonorrhea

Pregnant women with *Neisseria gonorrhoeae* infection may have localized infection such as cervicitis, urethritis, pharyngitis, or proctitis, but also appear to be at a somewhat increased risk for disseminated infection. Maternal infection is associated with a three-fold increased risk of preterm birth. Maternal genital infection may result in neonatal gonococcal conjunctivitis, pharyngitis, and neonatal sepsis and disseminated infection. Because of the risk of blindness in infants who develop conjunctivitis due to gonococcal infection, silver nitrate or antibiotic ointment are routinely administered for ophthalmic prophylaxis. Screening in the first and third trimester is recommended for women at high risk of infection, such as those with new partners, multiple partners, a previous STI, or in areas with a high prevalence of gonococcal infection. In pregnant women, diagnosis by nucleic amplification methods is preferred although culture should be used for rectal and pharyngeal specimens. The preferred treatment for localized infection is ceftriaxone 125 mg intramuscularly or cefixime 400 mg orally as a single dose. Azithromycin 2 g orally may be used in cases of cephalosporin allergy. Disseminated infection requires higher doses and more prolonged treated, dependent on the site of infection.

Diagnosis of infection in the infant should generally use culture methods.

Syphilis

Pregnancy does not alter the clinical course of syphilis in pregnant women, but there is a high risk of transmission of syphilis to the fetus at all stages of syphilis. The risk is greatest (60%) in primary and secondary syphilis, but remains high (40%) in early latent infection, and in latent maternal infection up to 4 years duration (10%). The risk of transmission becomes minimal in women infected for periods longer than 4 years.[156]

Syphilis causes spontaneous abortion, preterm birth, congenital malformations, and long-term neurologic deficits. Fetal abnormalities appear to be a consequence of the

immune response to treponemal organisms, and conversely, due to limited fetal inflammatory responses there are few signs of clinical disease in the fetus before 18 weeks gestation. As a consequence, there are few if any sequelae when treatment is instituted promptly for disease detected early in pregnancy. Syphilis is a disseminated infection, and untreated infection in a fetus after 18 weeks gestation leads to multiorgan disease. Hepatic involvement occurs early, and is associated with decreased fetal erythrocyte production and anemia, which can be followed by output failure with ascites, hydrops, and sometimes death. Infants viable at birth may have jaundice with petechiae or purpura, diffuse adenopathy, rhinitis (snuffles), pneumonia, myocarditis, and nephrosis. Syphilitic infection also alters placental function due to changes in the villi, which become thickened and club-shaped with evidence of vascular insufficiency due to endarteritis and stromal proliferation.

All pregnant women should be screened for syphilis with a treponemal or nontreponemal serologic test at the first prenatal visit, and preferably again at delivery. Women at high risk should also be screened at 28 weeks gestation. Women should be treated with benzathine penicillin, 2.4 million units intramuscularly as a single dose for early syphilis, and as a weekly dose for 3 weeks for syphilis greater than 1 year in duration. Penicillin-allergic women should be desensitized. The nontreponemal test should be repeated at 28–32 weeks gestation and at delivery, and at 6 and 12 months after treatment for primary or secondary syphilis, and at 6, 12, and 24 months after treatment for late latent syphilis.

Bacterial Vaginosis and Trichomoniasis

Bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV) infection occur almost exclusively in sexually active women. Sexual transmission has not been established for BV, and no single agent appears to be responsible for development of this syndrome, although multiple bacterial species have been evaluated. Both BV and TV infection cause increased vaginal secretions, often with an unpleasant odor. Women may complain of itching or dysuria, or be asymptomatic. In pregnancy, BV and TV infection have been associated with increased risk of preterm birth. Screening for BV at the first prenatal visit is recommended for asymptomatic pregnant women, but only if there is a history of preterm birth. Diagnosis is based on clinical findings and the presence of 'clue cells' on wet mount. Treatment with either metronidazole 500 mg orally twice daily or 250 mg orally three times daily, or with clindamycin 300 mg orally twice daily, may be given for a total of 7 days. Routine screening of asymptomatic women without a history of prior preterm birth is not recommended.[157] Prospective trials have yielded conflicting results regarding the benefit of treatment for asymptomatic women for prevention of preterm birth. A meta-analysis of 17 trials, of which three included women considered high risk because of previous preterm birth, suggested there was no significant effect of antibiotic treatment on preterm birth.[158] Routine screening for TV infection is not currently recommended.

Genital Warts

Genital warts may proliferate and grow larger and more friable during pregnancy, and may progress to neoplasm. Large lesions may interfere with delivery. In addition, human papilloma virus (HPV) types 6 and 11 can cause respiratory papillomatosis in infants and children. It is unknown whether infection is transmitted transplacentally or perinatally, and cesarean delivery is not recommended to prevent transmission. Imiquimod, podophyllin, and podophyllotoxin should not be used during pregnancy. If treatment is needed, the lesions should be treated with cryotherapy, trichloracetic acid, or surgery.

HIV

The CDC recommends that all women should be screened for HIV infection early in pregnancy, and again before 36 weeks if at high isk, unless testing is declined ('opt-out approach'). Universal testing is recommended, since some studies have found that more than one-third of women whose HIV infections were first detected during pregnancy were not aware of, or did not report, risk factors for HIV infection before testing.[159] Rapid HIV testing is recommended for women whose HIV status is unknown at the time of labor onset.

Recommendations for optimal management of HIV-infected pregnant women are updated regularly. The most recent Public Health Service recommendations (2008),[160] plus available data regarding safety of various antiretrovirals in pregnancy and management suggestions for various common clinical scenarios, are available at www.AIDSinfo.nih.gov. The 2008 recommendations are summarized in Table 47.7. These guidelines primarily address prevention of transmission of HIV-1; little information is available regarding management of HIV-2-infected mothers.

The goal of HIV management in pregnancy is to maximize the health of the mother, and to prevent maternal–fetal transmission of HIV. Initial evaluation of the HIV-infected pregnant woman should include an assessment of immune function and the need for prophylaxis against opportunistic infections. Treatment of pregnant women is complicated by the need to avoid drugs with teratogenic potential, particularly in the first trimester. Efavirenz, in particular, has been associated with central nervous system defects in animal studies and in some case reports, and an alternative agent substituted whenever possible even for women already taking a regimen that includes it. However, HAART should be offered to all HIV-positive women, since antiretroviral therapy has been shown to reduce congenital HIV transmission even when the mother's viral load is less than 1000 copies/ml.[161] Whenever

TABLE 47.7 Measures for prevention of mother-to-child HIV transmission

Newly diagnosed or previously untreated

Women with HIV RNA ≥ 1000 copies/ml
- Resistance testing prior to initiation of treatment
- Zidovudine-containing HAART – if possible delay until after first trimester

Women with HIV RNA <1000 copies/ml
- Zidovudine-containing HAART – if possible delay until after first trimester
- Consider discontinuing HAART postnatally; if NNRTI was used, stop NNRTI prior to NRTI to prevent emergence of NNRTI resistance

Previously known HIV infection

On HAART, mother chooses to continue
- Zidovudine-containing HAART regimen
- Fetal ultrasound second trimester for malformations if fetal exposure to efavirenz in the first trimester
- Resistance testing if persistently detectable HIV RNA

On HAART, mother chooses to stop
- Intrapartum/postpartum zidovudine
- Fetal ultrasound second trimester for malformations if fetal exposure to efavirenz in the first trimester

ALL HIV-infected pregnant women

- Monitor CD4 cell count at initial visit and every 3 months
- Measure HIV RNA at initial visit, 2–6 weeks after starting or changing HAART, monthly until undetectable, then every 2 months, and at 34–36 weeks gestation
- Avoid efavirenz in first trimester
- Avoid nevirapine in women with CD4 >250 cells/mm^3
- Monitor for hepatic dysfunction. Check transaminases and electrolytes monthly in the last trimester.
- Monitor women on protease inhibitors for glucose intolerance
- Fetal ultrasound first trimester to confirm gestational age
- Intravenous zidovudine should be given during labor even to women with evidence of resistance by genotyping
- Scheduled cesarean delivery if HIV RNA >1000 copies/ml near delivery
- Avoid artificial rupture of membranes, invasive monitoring, and forceps or vacuum extractor during delivery
- Avoid methergine (ergot) in women receiving protease inhibitors or efavirenz
- 6 week zidovudine prophylaxis of infants dosed by gestational age; consider additional agents if high maternal viral load or resistance. Should be started within 6–12 hours after birth
- Woman does not breastfeed

possible, women exposed to HAART during pregnancy should be entered in the Antiretroviral Pregnancy Registry (www.APRegistry.com).

Infants of untreated mothers have a 15–40% risk of congenital HIV transmission. HIV transmission can be minimized by administration of HAART combined with intrapartum and postpartum zidovudine. Intrapartum prophylaxis alone is not sufficient; although 30% of transmission occurs intrapartum, estimates are that 50% occurs in the period just prior to delivery, and 20% before 36 weeks. The period between 28 and 36 weeks gestation accounts for a significant proportion of transmission.[162] The risk for peripartum transmission is increased in preterm birth, and with prolonged rupture of the membranes. Elective cesarean delivery may reduce the risk of HIV transmission by as much as 50–70%, but is associated with increased risk of maternal complications including endometritis, sepsis, and pneumonia. Cesarean delivery is primarily recommended for women with persistently elevated viral load, or whose viral load is unknown.

In addition to reducing the risk of HIV transmission to the infant, antiretroviral therapy of the mother reduces the risk of infant death.[163] Combination antiretroviral therapy is the current standard of care,[160] although a number of regimens including zidovudine (AZT) alone, AZT plus lamivudine (3TC), and nevirapine alone for various durations during pregnancy, labor, and to the infant after birth have demonstrated at least partial efficacy.[164,165] Combination therapy including a protease inhibitor decreased congenital HIV transmission to 1.2% in comparison to 20% in infants of untreated women.[166] Regimens should generally include AZT since passage across the placenta is excellent. Dosing recommendations for AZT are given in Table 47.8. HAART prophylaxis should be started by the 28th week of gestation

TABLE 47.8 Intrapartum and postpartum dosing of zidovudine

Maternal/intrapartum

All HIV-positive mothers:
- 2 mg/kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg/kg body weight per hour
- Begin with labor onset, treat until delivery

Neonatal/postpartum

Term infants (≥35 weeks):
- 2 mg/kg body weight per dose given orally, OR
- 1.5 mg/kg body weight per dose given intravenously, begun within 6–12 hours or sooner after birth, then given every 6 hours
- Begin at birth, treat through age 6 weeks

30 weeks up to 35 weeks:
- 2 mg/kg body weight per dose given orally, OR
- 1.5 mg/kg body weight per dose given intravenously, begun within 6–12 hours or sooner after birth, then given every 12 hours; increased to every 8 hours at age 2 weeks
- Begin at birth, treat through age 6 weeks

< 30 weeks:
- 2 mg per kg body weight per dose given orally, OR
- 1.5 mg per kg body weight per dose given intravenously, begun within 6–12 hours or sooner after birth, then given every 12 hours; increased to every 8 hours at age 4 weeks
- Begin at birth, treat through age 6 weeks

in women who are not already receiving antiretroviral therapy. Resistance testing is recommended when therapy is initiated and for women whose viral load remains elevated. Antiretrovirals that should be avoided in pregnancy include efavirenz (teratogenicity), nevirapine (hepatic dysfunction in women with CD4 >250 cells/mm^3), and stavudine plus didanosine (lactic acidosis). Pregnant women receiving protease inhibitors may require increased doses in the third trimester.

Early intra-uterine infection with HIV is associated with intra-uterine growth retardation, microcephaly, and craniofacial abnormalities. In several cohort studies, infants of HIV-infected mothers have been shown to have increased morbidity and mortality whether or not they are infected with HIV, although the risk is highest in infants who are infected at birth or within the first 6 weeks of life. Maternal morbidity and mortality, absolute CD4+ T cell count of <350 cells/mm^3, and increased maternal viral load are predictors of infant morbidity and mortality. Infants most often present with pneumonia and sepsis.[167,168]

Breastfeeding contributes to transmission in 30–50% infants, and HIV-positive mothers should be advised not to breastfeed, even if receiving HAART.

HIV-positive women with chronic hepatitis B co-infection may benefit from a regimen that includes tenofovir plus 3TC or emtricitabine (FTC). These women must be monitored for hepatic toxicity. If antiretroviral therapy is discontinued postpartum, there is a risk of hepatitis flare.

Hepatitis A,B,C

Hepatitis A

Hepatitis A (HAV) is a very common infection caused by a small, non-enveloped RNA virus that is easily spread by a fecal–oral route. The incubation period is 15–50 days. Initial symptoms are flu-like, with fever, myalgias, and headache, followed by elevation of serum hepatic transaminases and jaundice. Fulminant infection may be accompanied by coagulopathy and signs of acute liver failure. HAV infection is rare in pregnancy in developed countries, occurring in about 1/1000.[169] Findings from a retrospective study suggest the risk of preterm labor and other pregnancy complications is increased when acute maternal HAV infection occurs in the second or third trimester.[170] HAV infection is diagnosed by detection of anti-HAV IgM in serum. The therapy is supportive, with bed rest, IV fluids, antiemetics, and vitamin K for coagulopathy. Perinatal transmission occurs during travel through birth canal. Prevention of HAV infection includes administration of inactivated vaccine, which is safe in pregnancy, to women traveling or at high risk, and intramuscular immunoglobulin if a known exposure occurs.

Hepatitis B

Hepatitis B virus (HBV) is a double stranded DNA virus that replicates using a reverse transcription step. Most transmission occurs through contact with blood and body fluids, and sexual transmission is well-recognized. The incubation

period is 2 to 4 months. Acute or active HBV infection is diagnosed by detection of hepatitis B surface antigen (HBsAg) in serum.

In addition to acute hepatitis, HBV infection carries the risk of chronic infection (5–10% of infections) with subsequent cirrhosis and liver dysfunction and the risk of hepatocellular carcinoma, which develops in up to 50% of chronic carriers. The risk of chronic infection is inversely related to the age of the individual when infection is acquired, and infants infected at birth have a 90% likelihood of developing chronic disease.

Acute HBV infection complicates 1–2 per 1000 pregnancies, and chronic HBV is found in 1% of pregnancies. The risk of transmission to the fetus is greatest when maternal acute HBV infection is acquired in the second (10%) and third (70%) trimesters, since these mothers are most likely to be shedding HBV at delivery. Mothers who are both HBeAg+ and HBsAg+ are most infectious. More than 95% of transmission to the infant occurs during labor and delivery. In the United States prior to routine screening and treatment of newborns, 4% of all acute and 25% of all chronic HBV infections were acquired in the perinatal period.[169] Because infants who acquire HBV are very likely to develop chronic infection, the CDC recommends that women at high risk for acquisition of HBV infection should receive HBV vaccine, which is safe in pregnancy. Women exposed to HBV, and infants of mothers who are HBsAg+, or who were diagnosed with HBV infection in pregnancy, should receive prophylaxis with HBV vaccine and hepatitis B immune globulin (HBIG). Some evidence suggests that administration of HBIG to HBeAg+/HBsAg+ women in the third trimester of pregnancy can prevent transmission of HBV to infants who acquire infection in utero rather during the birth process.[171]

All women should be tested for HBsAg at the first prenatal visit in each pregnancy, even if previously tested or vaccinated. Women who have not previously been screened or who are at high risk for hepatitis B (multiple partners, STD, intravenous drug use, HbsAg+ partner, clinical hepatitis) should be screened at delivery. Women at risk who are not seropositive should be vaccinated.

Hepatitis C

Hepatitis C virus (HCV) is an enveloped, single stranded RNA virus transmitted through transfusion or other contact with blood. Sexual transmission may occur but has not clearly been documented. HCV becomes chronic in >50% infections, and has a high association with hepatocellular carcinoma. Between 2 and 5% of pregnant women in the United States are infected with HCV.[169] Diagnosis of HCV is based on serologic testing, followed by confirmatory serologic testing or qualitative molecular testing for viral RNA. Pregnancy does not appear to modify the course of HCV in the mother. Acute HCV during pregnancy appears to be associated with some increased risk of preterm delivery, and infants are susceptible to infection during delivery because of exposure to infectious virus during the birth process. Vertical transmission occurs in 7% infants whose mothers are HCV RNA-positive, but not from mothers who are HCV RNA-negative. Cesarean delivery may not decrease transmission of HCV.[172] All pregnant women with a history of IV drug use, blood transfusion or organ transplantation before 1992 should be screened for hepatitis C infection with a serologic assay. Use of interferon (causes fetal growth retardation) and ribavirin (teratogenic effects) is contraindicated in pregnancy.

Group B streptococcus

Studies in the United States and Europe have found that between 10 and 30% of women of child-bearing age are colonized by group B streptococcus (GBS). Most pregnant women are asymptomatic, although a small number develop GBS urinary tract infection, chorioamnionitis or endometritis. Without prophylaxis, colonization can be demonstrated in over 40% of infants born to colonized mothers.[173] The majority of vertical transmission occurs during labor and passage through the birth canal. Intra-uterine infection of the fetus appears to follow ascending spread of GBS from the vagina. A small number of infants may be infected after swallowing infected amniotic fluid. GBS-infected infants may present with sepsis, pneumonia, meningitis, osteomyelitis or septic arthritis. Delivery at <37 weeks gestation, or prolonged membrane rupture, or maternal intrapartum temperature >99.5 °F (37.5 °C) increase the risk of early-onset GBS disease by 6.5 times.

Prior to implementation of the 2002 guidelines for universal screening and intrapartum treatment supported by the CDC,[174] the American College of Obstetrician sand Gynecologists (ACOG), and the American Academy of Pediatrics, the attack rate for Group B streptococcal neonatal sepsis and meningitis in the United States was 2 per 1000, with a 50% mortality.[175] During the 3 years (2003–2005) following implementation of the CDC guidelines, there was a 70% decrease in the rate of early (infants aged 0–6 days) neonatal infection, although the overall rate of invasive group B streptococcal disease increased. Intrapartum prophylaxis did not affect the rate of late (infants aged 7–89 days) infection. The major benefit of prophylaxis has been observed in white infants. By contrast, rates in black infants rose by 70% during 2003–2005.[176] In general, the incidence of invasive group B streptococcal infection is twice as high in blacks as in whites, and the relative risk is 4 to 5 times as high in infants and pregnant women.[177]

Per the 2002 guidelines, all pregnant women should be screened between 35 and 37 weeks gestation, or at labor if not yet screened. Women screened early should be retested after 4 weeks if they have not delivered. Specimens should be obtained from both the rectum and vagina, and tested for GBS, either by a culture method using a

selective enrichment broth, or by a nucleic acid amplification method. Women with GBS UTI do not need to be rescreened.

The 2002 recommendations are summarized in Table 47.9. Per the guidelines, an infant who was >38 weeks gestation, appears healthy, and whose mother received at least 4 hours of intrapartum prophylaxis before delivery may be discharged home after 24 hours if there are no other outstanding concerns, and a person who can comply with home observation will be present.

There are efforts under way to develop a vaccine to prevent invasive GBS disease. Recent CDC surveillance data suggests that a pentavalent conjugate vaccine including types Ia, Ib, II, III, and V, could prevent up to 96% of neonatal disease in the United States.[177]

Listeriosis

Infection with the Gram-positive bacillus *Listeria monocytogenes* is most often food-borne. It is reported to have the highest mortality rate of any food-borne pathogen, even when appropriate antibiotic therapy is given.[178] Because it is an intracellular pathogen, and is dependent on T cell-immunity for resolution of infection, serious illness occurs in individuals with compromised cell-mediated immunity. Up to one-third of reported cases of listeriosis occur in pregnant women, most frequently in the third trimester.[179] Although infection may cause maternal septicemia, most often it is apparent only as a flu-like illness, or as premature labor or decreased fetal movements.

The initial site of infection after ingestion is usually the intestine, followed by translocation and spread to the liver and spleen where replication occurs. Although the primary mode of infection of the placenta and gravid uterus is hematogenous, ascending infection from the vagina may also occur. *Listeria*, like other Gram-positive organisms, binds immune cells through TLR-2; TLR-2 receptors are also present on amniotic epithelial cells, decidual inflammatory cells, and placenta. Binding of *Listeria* to pregnancy-associated tissues may be mediated in part through the TLRs expressed by these cells, or might contribute to apoptotic cell death of placental tissues.

Once the uterus is infected, the organism evades non-specific innate and specific cell-mediated immune responses. Invasion factors such as listeriolysin O and phospholipase C allow the bacteria to escape from phagocytic vacuoles by forming pores in cell membranes, and causing lysis of the vacuole. *Listeria* is able to replicate in the cell cytosol, and to use intracellular actin polymerization to propel bacteria from one cell to another cell with minimal exposure to the extracellular environment.[178] *Listeria* also expresses surface proteins called internalins that enable the organism to invade nonphagocytic cells including placental syncytiotrophoblast and villous cytotrophoblast cells, as well as intestinal cells.[180]

The outcome of placental infection is pregnancy loss, fetal death, preterm birth or stillbirth.[181] A newborn exposed to *Listeria* may develop septicemia or meningoencephalitis. In some outbreaks, up to 63% of pregnancies complicated by maternal listeriosis terminated in fetal or neonatal death. Empiric treatment with ampicillin or amoxicillin may improve outcome.[181]

EMERGING INFECTIONS

Dengue

Dengue hemorrhagic fever (DHF) is a serious complication of infection with the mosquito-borne dengue fever virus, and is more likely to follow a primary dengue infection in pregnant than in nonpregnant women. DHF may be confused with pre-eclampsia, because of the symptoms of thrombocytopenia, liver dysfunction, capillary leak, edema, ascites, and decreased urine output.[182] Most pregnant women with dengue present in the third trimester. Dengue infection in the first trimester of pregnancy may be complicated by spontaneous abortion, and in the third trimester by premature delivery, and by severe and prolonged bleeding during surgical deliveries. The incidence of fetal death is increased. In DHF, increased vascular permeability and endothelial leakage damage the placenta, and may allow vertical transmission of virus. Fetal malformations do not appear to be associated with maternal infection.[183] However, exposure in utero may predispose the infant to DHF. Treatment is supportive, with intravenous fluid replacement and platelet transfusions as needed.[182] Pregnant women should avoid travel to areas of ongoing dengue transmission, particularly in the third trimester.

West Nile Virus (WNV)

West Nile virus is a mosquito-borne flavivirus that infects humans, other mammals including horses, dogs, cats, alpacas, and non-mammalian species such as birds and alligators. Many species of mosquito can transmit the virus. Infection of the placenta and transmission to the fetal has been shown in a murine model,[184] and vertical transmission of WNV with subsequent encephalitis was found in 3 of 72 live-born infants.[185]

However, a study by the same authors of birth outcomes following WNV infection in pregnant women in the United States has not clearly demonstrated the relationship to developmental abnormalities. Reports of outcomes following WNV infection during pregnancy have included cases of fetal growth retardation,[186] and a more dramatic case of chorioretinal scarring and brain abnormalities, including lissencephaly and severe white matter loss, in an infant born to a mother infected with WNV during the second trimester.[187]

TABLE 47.9 Intrapartum prophylaxis for prevention of early-onset GBS infection

Screen

- All pregnant women between 35 and 37 weeks gestation, unless GBS bacteriuria has been detected

Treat

- Women whose culture results are unknown but who have risk factors:
  - Delivery at <37 weeks gestation
  - Prolonged membrane rupture >18 hours
  - Maternal intrapartum temperature >38.0 °C
- Women with GBS bacteriuria during the current pregnancy
- Women who previously gave birth to an infant with invasive GBS

Do not treat

- Women with negative cultures obtained during the 5 weeks prior to delivery
  - GBS-colonized women undergoing planned cesarean deliveries who have not begun labor or had rupture of membranes

Regimens

- Recommended
  - Penicillin G, 5 million units intravenously × 1 dose, followed by 2.5 million units intravenously every 4 hours until delivery
- Alternative
  - Ampicillin 2 g intravenously × 1 dose, followed by 1 g intravenously every 4 hours until delivery
- Penicillin allergy
  - Low risk for anaphylaxis:
    - Cefazolin 2 g intravenously × 1 dose, followed by 1 g intravenously every 8 hours until delivery
  - High risk for anaphylaxis: GBS susceptible to erythromycin
    - Erythromycin 500 mg intravenously every 6 hours until delivery GBS susceptible to clindamycin
    - Clindamycin 900 mg intravenously every 8 hours until delivery GBS resistant to erythromycin and clindamycin
    - Vancomycin 1 g intravenously every 12 hours until delivery

Adapted from CDC, Prevention of perinatal group B Streptococcal disease. *MMWR* 2002;51(RR11);1-22.

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers including Lassa fever and Ebola appear to be more severe during pregnancy, and mortality is higher. For pregnant women infected with Lassa fever, the risk of death is highest in the third trimester. The placenta is thought to be a site for viral replication, and women improve rapidly after delivery or termination of pregnancy.[188] In Ebola virus infection, the risk of death is similar in all trimesters, and pregnant women are more likely to have hemorrhagic and neurologic complications.[189]

Lymphocytic Choriomeningitis Virus (LCMV)

LCMV is an arenavirus that is the cause of a zoonotic infection acquired from contact with rodents or their waste. In adults, infection causes fever, malaise, myalgias, anorexia, nausea, vomiting, pharyngitis, and adenopathy. CNS disease occurs after a period of improvement. Intra-uterine LCMV infection can cause fetal death, hydrocephalus, microcephaly or macrocephaly, chorioretinitis, and neurologic sequelae such as psychomotor retardation and deafness. Neurologic findings are highly variable, and may correlate with developmental stage at the time of infection. The diagnosis is made serologically.[190,191] Pregnant women should avoid rodents and their excreta.

Human Granulocytic Anaplasmosis (HGA, Previously Called Human Granulocytic Ehrlichiosis)

Only a few cases of infection in pregnant women by *Anaplasma phagocytophilum* (previously *Ehrlichia phagocytophilum*) have been described. In sheep and cows, infection in late pregnancy has been reported to cause stillbirth, abortion, and congenital infection. When recognized and treated, there do not appear to be adverse consequences in human pregnancy. In a recent report reviewing nine cases of HGA in women between 10 and 39 weeks gestation, pregnancy did not affect the severity of illness. Congenital infection was found in only one case, and all patients were treated successfully with either doxycycline or rifampin.[192]

Clostridium Difficile Infection (CDI)

Disease due to the anaerobic bacterium *Clostridium difficile* is most often manifested as diarrhea that may progress to

fulminant colitis, sepsis, and death. CDI usually occurs as a healthcare-associated infection, particularly in patients with disturbed bowel flora because of preceding antibiotic use or, rarely, inflammatory bowel disease. Prior to 2005, CDI was reported infrequently in pregnant women. However, in 2005–2006, 10 women with severe CDI were reported to the CDC.[193] Two of these women were infected by an apparently new hyper-virulent epidemic strain designated PCR ribotype 027.3 or North American Pulsed-Field type 1 (NAP1), which hyper-produces toxins A and B, and an additional product, binary toxin. Three of the pregnancies ended in stillbirths. Six women developed toxic megacolon, and five of those underwent colectomy. Three women ultimately died. Most of the women had not previously been admitted to the hospital, and in at least one case there was no known prior antimicrobial treatment, leading to a concern that pregnancy might be a predisposing factor for severe CDI. Th-1 cytokines have been proposed to play a role in resolution of CDI, and one hypothesis suggests that the decreased Th-1 response later in pregnancy might coincide with an increased susceptibility to CDI. Four additional cases of peripartum CDI, in two cases with the 'hyper-virulent' strain, have been reported recently.[194]

POTENTIAL AGENTS OF BIOTERRORISM

Smallpox

The last case of naturally occurring smallpox was reported from Somalia in 1977, but smallpox remains a concern because of its potential use as an agent of bioterrorism. In historical studies, mortality rates have generally been much higher in pregnant women, reportedly up to 63%.[195] A recent review of four large studies over the period from 1868 through 1962 found an overall case fatality rate in pregnant women of 34.3%, with risk increasing from an overall 22.9% in the first trimester to 40.5% in the third trimester.[196] Pregnant women are also more likely to develop hemorrhagic smallpox. Vaccination offers considerable protection against mortality, and the risk of death from smallpox infection appears to be 10-fold higher in unvaccinated as compared to previously vaccinated pregnant women.[195,196]

Acute maternal smallpox also has a devastating affect on pregnancy outcome, causing spontaneous abortion and premature termination of pregnancy. The overall proportion of abortion or preterm birth was 39.9%,[196] but has been reported to be up to 60–75%.[195] Over half of live births born to mothers infected in the second half of pregnancy die within the two weeks after delivery, and most within the first 72 hours. The risk of miscarriage and preterm birth were similarly elevated even in women with mild cases of smallpox. Prior vaccination does not appear to improve pregnancy outcome.[196]

Cellular immunity appears to be the most important aspect of the immune response determining outcome, since neutralizing antibodies develop early in primary infections and do not influence lesion size or affect survival. Animal models in non-pregnant inbred mice of experimental poxvirus infections with vaccinia or the murine poxvirus ectromelia have shown that a 'type 1' immune response and production of Th1 cytokines promote resistance to smallpox, but a 'type 2' response enhances pathogenesis.[195]

Smallpox vaccination of pregnant women is recommended only in the setting of a potential outbreak, since vaccination just before conception or during pregnancy can result, in rare instances, in fetal vaccinia. The risk is very small, and only about 50 cases have been documented, despite massive smallpox vaccination during eradication efforts.[197]

For the 376 women in the US military enrolled in the National Smallpox Vaccine in Pregnancy Registry from 2003 through 2006, the rates of pregnancy loss (11.9%), preterm birth (10.7%), and birth defects (2.8%), were not increased, and there were no cases of fetal vaccinia.[198]

ISSUES REGARDING ANTIBIOTIC MANAGEMENT IN PREGNANCY

Because most antimicrobial agents cross the placenta, drugs that could potentially have adverse effects on the fetus should be avoided in other than life-saving circumstances. An agent with a known safety profile should be used whenever possible. Currently, the FDA categorizes antimicrobials for use in pregnancy based on evidence of safety and risk as Category A (Studies of use by pregnant women without known adverse effects on fetus), Category B (Appear safe in animal studies, limited studies in pregnant women or appear safe in human studies although some problem in studies of pregnant animals), Category C (Little or no evidence regarding safety or harm in pregnant women), Category D (Evidence of harm in some cases, but benefit may outweigh risk in some circumstances), Category X (Risk is high, unlikely to be outweighed by benefit). The Food and Drug Administration (FDA) plans to change this classification system in the near future to be more clinically descriptive.

Most antibiotics are pregnancy Category B, such as the penicillins, including beta lactam/beta-lactamase inhibitor combinations, cephalosporins, aztreonam, nitrofurantoin, clindamycin, and aminoglycosides, and these drugs are generally considered safe in pregnancy. Sulfonamides and trimethoprim should be avoided when other agents are available. These drugs affect folate metabolism, potentially affecting first trimester neural tube development, and in the third trimester, sulfonamides can lead to neonatal

TABLE 47.10 Guidelines for vaccination of pregnant women

No contraindications

- Inactivated influenza
- Hepatitis B
- Tetanus-diphtheria (Td)
- Meningococcal (MPSV4)
- Rabies

Presumed low risk: use if high likelihood of disease exposure

- Hepatitis A
- Pneumococcal polysaccharide (PPV23)
- Inactivated polio vaccine
- Tetanus, diphtheria, pertussis (Tdap)

Unknown risk: use only if very high likelihood of disease exposure

- Anthrax
- Vaccinia (smallpox)
- Japanese encephalitis
- Yellow fever

Contraindicated

- Human papillomavirus
- Attenuated influenza
- Measles
- Mumps
- Rubella
- Attenuated polio vaccine
- Varicella
- Zoster
- BCG

Adapted from CDC and ACIP Guidelines, updated May 2007.

hyperbilirubinemia and kernicterus. In G6PD-deficient women, sulfonamides can cause hemolytic anemia that may be poorly tolerated in pregnancy. Ceftriaxone is also known to displace bilirubin from albumin, but this does not appear to limit its use in pregnant women.

Because GFR is increased by 30–50% in pregnancy, doses of some drugs such as aminoglycosides and ceftriaxone may require adjustment.[75] Monitoring serum levels may assist with dosing of vancomycin and aminoglycosides.

VACCINATION

There are no known risks to vaccination of pregnant women with bacterial vaccines or toxoids or with inactivated virus vaccine. Attenuated live vaccines should be avoided, since there is a potential risk for dissemination to the fetus. Accidental vaccination with a live-virus vaccine is not considered an indication for pregnancy termination. Guidelines from the CDC were updated in 2007 (see Table 47.10).

References

1. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the United States, 1991–1997. *Obstet Gynecol* 2003;101:289–96.
2. MacKay AP, Berg CJ, King JC, Duran C, Chang J. Pregnancy-related mortality among women with multifetal pregnancies. *Obstet Gynecol* 2006;107:563–68.
3. Martin JA, Hamilton BE, Sutton PD, *et al*. Centers for Disease Control and Prevention National Center for Health Statistics, National Vital Statistics System. Birth: final data for 2005. *Natl Vital Stat Rep* 2007;56(6):1–103.
4. Ledger WJ. Perinatal infections and fetal/neonatal brain injury. *Curr Opin Obstet Gynecol* 2008;20:120–24.
5. Shim SS, Romero R, Hong JS, *et al*. Clinical significance of intraamniotic inflammation in patients with preterm premature rupture of membranes. *Am J Obstet Gynecol* 2004;191:1339–45.
6. Goldenberg RI, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:73–82.
7. Gibbs RS. The origins of stillbirth: infectious diseases. *Semin Perinatol* 2002;26(1):75–78.
8. MacDorman MF, Hoyert DL, Martin JA, Munson ML, Hamilton BE. Fetal and perinatal mortality, United States, 2003. *Natl Vital Stat Rep* 2007;55(6):1–17.
9. Zupan J, Ohman EA. *Neonatal and Perinatal Mortality: Country, Regional and Global Estimates*. Geneva: World Health Organization; 2006, www.who.int/making_pregnancy_safer/publications/neonatal.pdf.
10. Spellberg B, Edwards JE Jr. Type 1/Type 2 immunity in infectious diseases. *Clin Infect Dis* 2001;32:76–102.
11. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenom? *Immunol Today* 1993;14:353–56.
12. Sargent IL, Borzychowski AM, Redman CWG. NK cells and human pregnancy – an inflammatory view. *Trends Immunol* 2006;27:399–404.
13. Sacks G, Sargent I, Redman C. An innate view of human pregnancy. *Immunol Today* 1999;20:114–18.
14. Mellor AL, Munn D. Policing pregnancy: tregs help keep the peace. *Trends Immunol* 2004;25:563–65.
15. Saito S, Nakashima A, Myojo-Higuma S, Shiozaki A. The balance between cytotoxic NK cells and regulatory NK cells in human pregnancy. *J Reprod Immunol* 2008;77:14–22.
16. Bachy V, Williams DJ, Ibrahim MAA. Altered dendritic cell function in normal pregnancy. *J Reprod Immunol* 2008;78:11–21.
17. Christiaens I, Zaragoza DB, Guilbert L, Robertson SA, Mitchell BF, Olson DM. Inflammatory processes in preterm and term parturition. *J Reprod Immunol* 2008;79:50–57.
18. Goerdt S, Orfanos CE. Other functions, other genes: alternative activation of antigen-presenting cells. *Immunity* 1999;10:137–42.
19. Hunt JS, Jadhav L, Chu W, Geraghty DE, Ober C. Soluble HLA-G circulates in maternal blood during pregnancy. *Am J Obstet Gynecol* 2000;183:682–88.
20. Carosella ED, Rouas-Freiss N, Paul P, Dausset J. HLA-G: a tolerance molecule from the major histocompatability complex. *Immunol Today* 1999;20:60–62.

21. Carosella ED, Moreau P, Le Maoult J, Le Discorde M, Dausset J, Rouas-Freiss N. HLA-G molecules: from maternal-fetal tolerance to tissue acceptance. *Adv Immunol* 2003;81:199–252.
22. Lin A, Xu H, Yan W. Modulation of HLA expression in human cytomegalovirus immune evasion. *Cell Mol Immunol* 2007;4:91–98.
23. Schust DJ, Tortorella D, Ploegh HL. HLA-G and HLA-C at the feto-maternal interface: lessons learned from pathogenic viruses. *Semin Cancer Biol* 1999;9:37–46.
24. Moraes-Pinto MI, Vince GS, Flanagan BF, Hart CA, Johnson PM. Localization of IL-4 and IL-4 receptors in the human term placenta, deciduas, and amniochorionic membranes. *Immunology* 1997;90:87–94.
25. Roth I, Corry DB, Locksley RM, Abrams JS, Litton MJ, Fisher SJ. Human placental cytotrophoblasts produce the cytokine interleukin 10. *J Exp Med* 1996;184:539–48.
26. Dungy LJ, Siddiqi TA, Khan S. Transforming growth factor-beta 1 expression during placental development. *Am J Obstet Gynecol* 1991;165:853–57.
27. Ando N, Hirahara F, Fukushima J, *et al*. Minaguchi H. Differential gene expression of TGF-beta isoforms and TGF-beta receptors during the first trimester of pregnancy at the human maternal-fetal interface. *Am J Reprod Immunol* 1998;40:48–56.
28. Ayatollahi M, Geramizadeh B, Yazdani M, Azarpira N. Effect of the immunoregulatory cytokines on successful pregnancy depends upon the control of graft rejection mechanisms. *Transplant Proc* 2007;39:244–45.
29. Motrán CC, Lopez Diaz F, Gruppi A, Slavinn D, Chatton B, Bocco JL. Human pregnancy-specific glycoprotein 1a (PSG1a) induces alternative activation in human and mouse monocytes and suppresses the accessory cell-dependent T cell proliferation. *J Leukoc Biol* 2002;72:512–21.
30. Holmlund U, Cebers G, Dahlfors AR, *et al*. Expression and regulation of the pattern recognition receptors Toll-like receptor-2 and Toll-like receptor-4 in the human placenta. *Immunology* 2002;107:145–51.
31. Abrahams VM, Mor G. Toll-like receptors and their role in the trophoblast. *Placenta* 2005;26:540–47. Review.
32. Rindsjö E, Holmlund U, Sverremark-Ekström E, Papadpgiannakis N, Scheynius A. Toll-like receptor-2 expression in normal and pathologic human placenta. *Hum Pathol* 2007;38:468–73.
33. Aflatoonian R, Fazeli A. Toll-like receptors in female reproductive tract and their menstrual cycle-dependent expression. *J Reprod Immunol* 2008;77:7–13.
34. Forest MG. Pituitary gonadotrophin and sex steroid secretion during the first two years of life. In: MM Grumbach, PC Sizonenko, ML Aubert, eds. *Control of the Onset of Puberty*. Baltimore, MD: Williams and Wilkins; 1990.
35. Clarke AG, Kendall MD. The thymus in pregnancy: the interplay of neural, endocrine and immune influences. *Immunol Today* 1994;15:545–52.
36. Medina KL, Kincade PW. Pregnancy-related steroids are potential negative regulators of B lymphopoiesis. *Proc Natl Acad Sci U S A* 1994;91:5382–86.
37. Medina KL, Smithson G, Kincade PW. Suppression of B lymphopoiesis during normal pregnancy. *J Exp Med* 1993;178:1507–15.
38. Lutton B, Callard I. Evolution of reproductive-immune interactions. *Integ Compar Biol* 2006;46:1060–71.
39. Piccinni MP, Scaletti C, Maggi E, Romagnani S. Role of hormone-controlled Th1-and Th2-type cytokines in successful pregnancy. *J Neuroimmunol* 2000;109:30–33.
40. Ehring GR, Kerschbaum HH, Eder C, *et al*. A nongenomic mechanism for progesterone-mediated immunosuppression: inhibition of K+ channels, Ca2+ signaling, and gene expression in T lymphocytes. *J Exp Med* 1998;188:1593–602.
41. Piccinni MP, Giudizi MG, Biagiotti R, *et al*. Progesterone favors the development of human T helper cells in producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *J Immunol* 1995;155:128–33.
42. Arck P, Hansen PJ, Mulac Jericevic B, Piccinni MP, Szekeres-Bartho J. Progesterone during pregnancy: endocrine-immune cross-talk in mammalian species and the role of stress. *Am J Reprod Immunol* 2007;58:268–79.
43. Druckmann R, Druckmann MA. Progesterone and the immunology of pregnancy. *J Steroid Biochem Mol Biol* 2005;97:389–96.
44. Polanczyk MJ, Carson BD, Subramanian S, *et al*. Cutting edge: estrogen drives expansion of the CD4+CD25+ regulatory T cell compartment. *J Immunol* 2004;173:2227–30.
45. Roberts CW, Walker W, Alexander J. Sex-associated steroids and immunity to protozoan parasites. *Clin Micro Rev* 2001;14:473–88.
46. Furr PM, Taylor-Robinson D. Oestradiol-induced infection of the genital tract of female mice by *Mycoplasma hominis*. *J Gen Microbiol* 1989;135:2743–49.
47. Furr PM, Taylor-Robinson D. The establishment and persistence of *Ureaplasma urealyticum* in oestradiol-treated female mice. *J Med Microbiol* 1989;29:111–14.
48. Kaushic C, Zhou F, Murdin AD, Wira CR. Effects of estradiol and progesterone on susceptibility and early immune responses to *Chlamydia trachomatis* infection in the female genital tract. *Infect Immun* 2000;28:4297–316.
49. MacMurray RW. Estrogen, prolactin, and autoimmunity: actions and interactions. *Int Immunopharmacol* 2001;1:995–1008.
50. Kapoor N, Sankaran S, Hyer S, Shehata H. Diabetes in pregnancy: a review of current evidence. *Curr Opin Obstet Gynecol* 2007;19:586–90.
51. Lao TT, Chan BC, Leung WC, Ho LF, Tse KY. Maternal hepatitis B infection and gestational diabetes mellitus. *J Hepatol* 2007;47:46–50.
52. Lucas MJ. Diabetes complicating pregnancy. *Obstet Gynecol Clin North Am* 2001;28:513–36.
53. Stamler EF, Cruz ML, Mimouni F, *et al*. High infectious morbidity in pregnant women with insulin-dependent diabetes: an understated complication. *Am J Obstet Gynecol* 1990;163:1217–21.
54. Chaim W, Bashiri A, Bar-David J, Shoham-Vardi I, Mazor M. Prevalence and clinical significance of postpartum endometritis and wound infection. *Infect Dis Obstet Gynecol* 2000;8:77–82.
55. Schneid-Kofman N, Sheiner E, Levy A, Holcberg G. Risk factors for wound infection following cesarean deliveries. *Int J Gynaecol Obstet* 2005;90:10–15.
56. Piper JM, Georgiou S, Xenakis EM, Langer O. Group B streptococcus infection rate unchanged by gestational diabetes. *Obstet Gynecol* 1999;93:292–96.

57. Ovalle A, Levancini M. Urinary tract infections in pregnancy. *Curr Opinion Urol* 2001;11:55–59.
58. Novak KF, Taylor GW, Dawson DR, Ferguson JE 2nd, Novak MJ. Periodontitis, and gestational diabetes mellitus: exploring the link in NHANES III. *J Publ Health Dent, Summer* 2006;66:163–68.
59. Fallarino F, Grohman U, Hwang KW, *et al*. Modulation of tryptophan catabolism by regulatory T cells. *Nat Immunol* 2003;4:1206–12.
60. Trowsdale J, Betz AG. Mother's little helpers: mechanisms of maternal-fetal tolerance. *Nat Immunol* 2006;7:241–46.
61. Krejci CB, Bissada NF. Women's health issues and their relationship to periodontitis. *J Am Dent Assoc* 2002;133:323–29.
62. Patterson TF, Andriole VT. Detection, significance, and therapy of bacteriuria in pregnancy. *Infect Dis Clin North Am* 1997;11:593–608.
63. Connolly A, Thorp JM. Urinary tract infections in pregnancy. *Urol Clin North Am* 1999;26:779–87.
64. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am* 2007;34:35–42.
65. Smaill F. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2007(2), CD000490. Review.
66. Ramsey PS, Ramin KD. Pneumonia in pregnancy. *Obstet Gynecol Clin North Am* 2001;28:553–59.
67. Cole DE, Taylor TL, McCullough DM, Shoff CT, Derdak S. Acute respiratory distress syndrome in pregnancy. *Crit Care Med* 2005;33(Suppl. 10):S269–78.
68. Bánhidy F, Acs N, Puhó EH, Czeizel AE. Maternal acute respiratory infectious diseases during pregnancy and birth outcomes. *Eur J Epidemiol* 2008;23:29–35.
69. Bakardjiev AI, Theriot JA, Portnoy DA. *Listeria monocytogenes* traffics from maternal organs to the placenta and back. *PLoS Pathog* 2006;2:e66.
70. Gilstrap LC, Ramin SM. Urinary tract infections during pregnancy. *Obstet Gynecol Clin North Am* 2001;28:581–91.
71. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005;40:643–54.
72. Rouse DJ, Andrews WW, Goldenberg RL, Owen J. Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: a cost effectiveness and cost–benefit analysis. *Obstet Gynecol* 1995;86:119–23.
73. Hill JB, Sheffield JS, McIntire DD, Wendel GD. Acute pyelonephritis in pregnancy. *Obstet Gynecol* 2005;105:18–23.
74. Towers CV, Kaminskas CM, Garite TJ, Nageotte MP, Dorchester W. Pulmonary injury associated with antepartum pyelonephritis: can patients at risk be identified? *Am J Obstet Gynecol* 1991;164:974–78.
75. PopovićJ, GrujićZ, Sabo A. Influence of pregnancy on ceftriaxone, cefazolin, gentamicin pharmacokinetics. *J Clin Pharm Ther* 2007;32:595–602.
76. Le J, Briggs GG, McKeown A, Bustillo G. Urinary tract infections during pregnancy. *Ann Pharmacother* 2004;38:1692–16701. Review.
77. Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. *Mol Nutr Food Res* 2007;51:738–45.
78. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? *Am J Obstet Gynecol* 1989;161:657–62.
79. Rigby FB, Patorek JG. Pneumonia during pregnancy. *Clin Obstet Gynecol* 1996;39:107–19.
80. Goodnight WH, Sper DE. Pneumonia in pregnancy. *Crit Care Med* 2005;33(Suppl. 10):S390–97.
81. Zeeman GG, Wendel GD, Cunningham FG. A blueprint for obstetrical critical care. *Am J Obstet Gynecol* 2003;188:532–36.
82. Tan MP, Koren G. Chickenpox in pregnancy: revisited. *Reprod Toxicol* 2006;21:410–20.
83. Chapman S, Duff P. Varicella in pregnancy. *Semin Perinatol* 1993;17:403–9.
84. Haake DA, Zakowski PC, Haake DL. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults. *Rev Infect Dis* 1990;12:788–98.
85. Mullooly JP, Barker WH, Nolan TF. Risk of acute respiratory disease among pregnant women during influenza A epidemics. *Public Health Rep* 1986;101:205–11.
86. Wong SF, Chow KM, Leung TN, *et al*. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol* 2004;191:292–97.
87. Ormerod P. Tuberculosis in pregnancy and the puerperium. *Thorax* 2001;56:494–99.
88. Espinal MA, Reingold AL, Lavandera M. Effect of pregnancy on risk of developing active tuberculosis. *J Infect Dis* 1996;173:488–91.
89. Tripathy SN, Tripathy SN. Tuberculosis, and pregnancy. *Int J Gynaecol Obstet* 2003;80:247–53.
90. Centers for Disease Control and Prevention. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):1–77.
91. Stevens DA. Coccidioidomycosis. *N Engl J Med* 1995;332:1077–82.
92. Rosenstein NE, Emery KW, Werner SB, *et al*. Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern County, California, 1995–1996. *Clin Infect Dis* 2001;32:708–15.
93. Hooper JE, Lu Q, Pepkowitz SH. Disseminated coccidioidomycosis in pregnancy. *Arch Pathol Lab Med* 2007;131:652–55.
94. Udagawa H, Oshio Y, Shimuzu Y. Serious group A streptococcal infection around delivery. *Obstet Gynecol* 1999;94:153–57.
95. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. *Cochrane Database Syst Rev* 2004;4, CD001067. Review.
96. Maberry MC, Gilstrap LC 3rd, Bawdon R, Little BB, Dax J. Anaerobic coverage for intra-amnionic infection: maternal and perinatal impact. *Am J Perinatol* 1991;8:338–41.
97. Tran SH, Cheng YW, Kaimal AJ, Caughey AB. Length of rupture of membranes in the setting of premature of membranes at term and infectious maternal morbidity. *Am J Obstet Gynecol* 2008;198(700):e1–e5.
98. Bobitt JR, Hayslip CC, Damato JD. Amniotic fluid infection as determined by transabdominal amniocentesis in patients with intact membranes in premature labor. *Am J Obstet Gynecol* 1981;140:947–952.
99. Ledger WJ. Post-partum endomyometritis diagnosis and treatment: a review. *J Obstet Gynaecol Res* 2003;29:364–373.

100. Smaill F, Hoffmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database Syst Rev* 2002;3, CD000933. Review.
101. Tita ATN, Hauth JC, Grimes A, Owen J, Stamm AM, Andrews WW. Decreasing incidence of postcesarean endometritis with extended-spectrum antibiotic prophylaxis. *Obstet Gynecol* 2008;11:51–56.
102. Shannon C, Brothers LP, Philip NM, Winikoff B. Infection after medical abortion: a review of the literature. *Contraception* 2004;70:183–190.
103. Fischer M, Bhatnagar J, Guarner J, *et al*. Fatal toxic shock syndrome associated with *Clostridium sordellii* after medical abortion. *N Engl J Med* 2005;353:2352–2360.
104. Cohen AL, Bhatnagar J, Reagan S, *et al*. Toxic shock associated with Clostridium sordellii and Clostridium perfringens after medical and spontaneous abortion. *Obstet Gynecol* 2007;110:1027–1033.
105. Aronoff DM, Hao Y, Chung J, *et al*. Misoprostol impairs female reproductive immunity against *Clostridium sordelli*. *J Immunol* 2008;180:8222–8230.
106. Livingston JC, Llata E, Rhinehart E, *et al*. Gentamicin and clindamycin therapy in postpartum endometritis: the efficacy of daily dosing versus dosing every 8 hours. *Am J Obstet Gynecol* 2003;188:149–152.
107. Brumfield CG, Hauth JC, Andrews WW. Puerperal infection after cesarean delivery: evaluation of a standardized protocol. *Am J Obstet Gynecol* 2000;182:1147–1151.
108. Olsen MA, Butler AM, Willers DM, Devkota P, Gross GA, Fraser VJ. Risk factors for surgical site infection after low transverse cesarean section. *Infect Control Hosp Epidemiol* 2008;29:477–484.
109. Martens MG, Kolrud BL, Faro S, Maccato M, Hammill H. Development of wound infection or separation after cesarean delivery, prospective evaluation of 2431 cases. *J Reprod Med* 1995;40:171–175.
110. Goepfert AR, Guinn DA, Andrews WW, Hauth JC. Necrotizing fasciitis after cesarean delivery. *Obstet Gynecol* 1997;89:409–412.
111. Michie C, Lockie F, Lynn W. The challenge of mastitis. *Arch Dis Child* 2003;88:818–821.
112. I. Semmelweis, The Etiology, the Concept, and the Prophylaxis of Childbed Fever: Classics of Obstetrics and Gynecology Library [translated by Frank P. Murphy]. New York: Division of Gryphon Editions; 1990:355–400.
113. Kar P, Jilani N, Husain SA, *et al*. Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? *Am J Gastroenterol* 2008;103:2495–2501.
114. Kumar RM, Uduman S, Rana S, Kochiyil JK, Usmani A, Thomas L. Seroprevalence and mother-to-infant transmission of hepatitis E virus among pregnant women in the United Arab Emirates. *Eur J Obstet Gynecol Reprod Biol* 2001;100:9–15.
115. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E infection. *Ann Intern Med* 2007;147:28–33.
116. Rodriguez-Morales AJ, Barbella RA, Case C, *et al*. Intestinal parasitic infections among pregnant women in Venezuela. *Infect Dis Obstet Gynecol* 2006:231–325.
117. Shah OJ, Robanni I, Khan F, Zargar SA, Javid G. Management of biliary ascariasis in pregnancy. *World J Surg* 2005;29:1294–1298.
118. Menéndez C, D'Allessandro U, ter Kuile FO. Reducing the burden of malaria in pregnancy by preventive strategies. *Lancet Infect Dis* 2007;7:126–135. Review.
119. Beeson JG, Rogerson SJ, Cooke BM. Adhesion of *Plasmodium falciparum*-infected erythrocytes to hyaluronic acid in placental malaria. *Nat Med* 2000;6:86–90.
120. Rogersonn SJ, Hviid L, Duffy PE, Leke RFG, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. *Lancet Infect Dis* 2007;7:105–117.
121. Duffy PE, Fried M. Malaria during pregnancy: parasites, antibodies, and chondroitan sulphate A. *Biochem Soc Trans* 1999;27:478–482.
122. Gamain B, Smith JD, Viebig NK, Gysin J, Scherf A. Pregnancy-associated malaria: parasite binding, natural immunity and vaccine development. *Int J Parasitol* 2007;37:273–283.
123. Bouyou MK, Adegnika AA, Agnandi ST, *et al*. Cortisol and susceptibility to malaria during pregnancy. *Microbes Infect* 2005;7(11-12):1217–1223.
124. Ned RM, Moore JM, Chaisavaneeyakorn S, Udhayakumar V. Modulation of immune responses during HIV-malaria coinfection in pregnancy. *Trends Parasitol* 2005;21:284–291.
125. Newman RD, Robalo M, Quakyi I. Malaria during pregnancy: epidemiology, current prevention strategies, and future directions. *Emerg Infect Dis [serial on the Internet]* 2004 November;1, Available from www.cdc.gov/ncidod/EID/vol10no11/04-0624_09.htm.
126. Friedman JF, Mital P, Kanzaria HK, Olds GR, Kurtis JD. Schistosomiasis and pregnancy. *Parasitol* 2007;23:159–164.
127. Rorman E, Zamir CS, Rilkis I, Ben-David H. Congenital toxoplasmosis – prenatal aspects of *Toxoplasma gondii* infection. *Reprod Toxicol* 2006;21:458–472.
128. Sukthana Y. Toxoplasmosis: beyond animals to humans. *Trends Parasitol* 2006;22:137–142.
129. Silveira C, Ferreira R, Muccioli C, Nussenblatt R, Belfort R. Toxoplasmosis transmitted to a newborn from the mother infected 20 years earlier. *Am J Opthalmol* 2003;136:370–371.
130. Kodjikian L, Hoigne I, Adam O, *et al*. Vertical transmission of toxoplasmosis from a chronically infected immunocompetent woman. *Pediatr Infect Dis J* 2004;23:272–274.
131. Castillo-Solorzano C, Marsigli C, Bravo Alcantara P, *et al*. Progress toward elimination of rubella and congenital rubella syndrome – the Americas, 2003–2008. *MMWR* 2008;57(43):1176–1179.
132. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982;ii:781–784.
133. Plotkin SA. The history of rubella and rubella vaccination leading to elimination. *Clin Infect Dis* 2006;43(Suppl. 3):S164–S168.
134. Rahav G, Gabbay R, Ornoy A, *et al*. Primary versus nonprimary cytomegalovirus infection during pregnancy, Israel. *Emerg Infect Dis* 2007;13:1791–1793.
135. Revello MG, Gerna G. Pathogenesis and prenatal diagnosis of human cytomegalovirus infection. *J Clin Virol* 2004;29:71–83.
136. Ornoy A, Diav-Citrin O. Fetal effects of primary and secondary cytomegalovirus infection in pregnancy. *Reprod Toxicol* 2006;21:399–409.

137. Schleiss MR. Congenital cytomegalovirus infection: update on management strategies. *Curr Treat Opt Neurol* 2008;10:186–192.
138. Bale JF, Mier L, Petheram SJ. Congenital cytomegalovirus infection. *Curr Treat Opt Neurol* 2002;4:225–230.
139. Sauerbrei A, Wutler P. Herpes simples and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Herpes simplex virus infections. *Med Microbial Immunol* 2007;196:89–94.
140. Peacock JE, Sarubbi FA. Disseminated Herpes simplex infection during pregnancy. *Obstet Gynecol* 1983;61(Suppl. 3):13S–18S.
141. Hutto C, Arvin A, Jacobs R, *et al*. Intrauterine herpes simplex virus infection. *J Pediatr* 1987;110:97–101.
142. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. *Cochrane Database Syst Rev* 2008:1, CD004946. Review.
143. Jensen IP, Thorsen P, Jeune B, Moller BR, Vesterqaard BF. An epidemic of parvovirus B19 in a population of 3,596 pregnant women: a study of sociodemographic and medical risk factors. *BJOG* 2000;107:637–643.
144. Tolvesnstam T, Papadogiannakis N, Norbek O, Petersson K, Broliden K. Frequency of human parvovirus B19 infection in intrauterine fetal death. *Lancet* 2001;357:1494–1497.
145. Rodis JF, Borgida AF, Wilson M, *et al*. Management of parvovirus infection in pregnancy and outcomes of hydrops: a survey of members of the Society of Perinatal Obstetricians. *Am J Obstet Gynecol* 1998;179:985–988.
146. Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. *Prenat Diagn* 2004;24:513–518.
147. Miller E, Fairley CK, Cohen BJ, Seng C. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *Br J Obstet Gynaecol* 1998;105:174–188.
148. Rodis JF, Rodner C, Hansen AA, Borgida AF, Deoliveira I, Shulman Rosengren S. Long term outcome of children following maternal human parvovirus B19 infection. *Obstet Gynecol* 1998;91:125–128.
149. Nagel HTC, de Haan TR, Vandenbussche FPHA, Oepkes D, Walter FJ. Long-term outcome after fetal transfusion for hydrops associated with parvovirus infection. *Obstetr Gynecol* 2007;109:42–47.
150. Weigel-Kelley KA, Yoder MC, Srivastava A. Alpha5-beta1 integrin as a cellular coreceptor for human parvovirus B19: requirement of functional activation of β1 integrin for viral entry. *Blood* 2003;102:3927–3933.
151. Munakata Y, Saito-ito T, Kumura-Ishii K, *et al*. Ku80 autoantigen as a cellular coreceptor for human parvovirus B19 infection. *Blood* 2005;106:3449–3456.
152. Söderlund-Venermo M, Hokynar K, Nieminen J, Rautakorpi H, Hedman K. Persistence of human parvovirus B19 in human tissues. *Pathol Biol (Paris)* 2002;50:307–316.
153. Sauerbrei A, Wutler P. Herpes simples and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 2. Varicella-zoster virus infections. *Med Microbial Immunol* 2007;196:95–102.
154. Workowski A, Berman SM. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2006. *MMWR* 2006;55(No. RR-11).
155. American College of Obstetricians and Gynecologists: ACOG Committee Opinion. Primary and preventive care: periodic assessments. *Obstet Gynecol* 2003;102:1117–1124.
156. Johnson HL, Erbelding EJ, Ghanem KG. Sexually transmitted infections during pregnancy. *Curr Infect Dis Rep* 2007;9:125–133.
157. US Preventive Services Task Force. Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;148:214–222.
158. Simcox R, Sin W-TA, Seed PT, Briley A, Shennan AH. Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. *Austral N Z J Obstet Gynaecol* 2007;47:368–377.
159. Favia A, Fiore JR, Pastore G. Newly diagnosed HIV-1 infections in pregnancy: evidences from a cohort study in southeastern Italy. *Eur J Epidemiol* 2004;19:391–393.
160. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008;1-139. Available at www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. (Accessed December 06, 2009.)
161. Ioannidis JP, Abrams EJ, Ammann A, *et al*. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis* 2001;183:539–545.
162. Lallemant M, Jourdain G, Le Couer S, *et al*. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med* 2000;343:982–991.
163. Jamieson DJ, Clark J, Koutis AP, *et al*. Reommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States. *Am J Obstet Gynecol* 2007;197(Suppl. 3):S26–S32.
164. Suksomboon N, Poolsup N, Ket-Aim S. Systematic review of the efficacy of antiretroviral therapies for reducing the risk of mother to chills transmission of HIV infection. *J Clin Pharm Ther* 2007;32:293–311.
165. Volmink J, Siegfrid NL, van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev* 2007;1, CD003510. Review.
166. Cooper ER, Charurat M, Mofenson L, *et al*. Women and Infant's Transmission Study Group. *J Acquir Immune Defic Syndr* 2002;29:484–494.
167. Kuhn L, Kasonde P, Sinkala M, *et al*. Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? *Clin Infect Dis* 2005;41:1654–1661.
168. Chilongozi D, Wang L, Brown L, *et al*. HIVNT 024 Study Team. Morbidity and mortality among a cohort of human immunodeficiency virus type 1-infected and -unifected pregnant women and their infants from Malawi, Zambia and Tanzania. *Pediatr Infect Dis J* 2008;27:808–814.
169. Magriples U. Hepatitis in pregnancy. *Semin Perinatol* 1998;22:112–117.
170. Elinav E, Ben-Dov IZ, Shapira Y, *et al*. Acute hepatitis a infection in pregnancy is associated with high rates of

gestational complications and preterm labor. *Gastroenterol* 2006;130:1129–1134.
171. Xiao XM, Li AZ, Chen X, Zhu YK, Miao J. Prevention of vertical hepatitis B transmission by hepatitis B immunoglobulin in the third trimester of pregnancy. *Int J Gynecol Obstet* 2007;96:167–170.
172. McMenamin MB, Jackson AD, Lambert J, *et al*. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 5559 mother-infant pairs. *Am J Obstet Gynecol* 2008;199(315):e1–e5.
173. Sensini A, Tissi L, Verducci N, *et al*. Carriage of group B *Streptococcus* in pregnant women and newborns: a 2-year study at Perugia General Hospital. *Clin Microbiol Infect* 1997;3:324–328.
174. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Centers for Disease Control and Prevention. Prevention of perinatal group B Streptococcal disease. *MMWR* 2002;51(RR11):1–22.
175. Larsen JW, Sever JL, Group B. streptococcus and pregnancy: a review. *Am J Obstet Gynecol* 2008;198:440–448.
176. Centers for Disease Control and Prevention. Perinatal group B streptococcal disease after universal screening recommendations – United States, 2003–2005. *MMWR* 2007;56(28):701–705.
177. Phares CR, Lynfield R, Farley MM, *et al*. Epidemiology of invasive group B streptococcal disease in the United States 1999–2005. *JAMA* 2008;299:2056–2065.
178. Orndorff PE, Hamrick TS, Smoak IW, Havell EA. Host and bacterial factors in listeriosis pathogenesis. *Vet Microbiol* 2006;144:1–15.
179. Gellin BG, Broome CV, Bibb WF, Weaver RE, Gaventa S, Macola L. The epidemiology of listeriosis in the United States – 1986. Listeriosis Study Group. *Am J Epidemiol* 1991;133:392–401.
180. Seveau S, Pizarro-Cerda J, Cossart P. Molecular mechanisms exploited by *Listeria monocytogenes* during host cell invasion. *Microbes Infect* 2007;9:1167–1175.
181. Craig S, Permezel M, Doyle L, Mildenhall L, Garland S. Perinatal infection with *Listeria monocytogenes*. *Aust N Z J Obstet Gynaecol* 1996;36:286–290.
182. Malhotra N, Chanana C, Kumar S. Dengue infection in pregnancy. *Int J Gynecol Obstet* 2006;94:131–132.
183. Waduge R, Malavige GN, Pradeepan M, Wijeyaratne CN, Fernando S, Seneviratne SL. Dengue infections during pregnancy: a case series from Sri Lanka and review of the literature. *J Clin Virol* 2006;37:27–33.
184. Julander JG, Winger QA, Rickfords LF, *et al*. West Nile virus infection of the placenta. *Virology* 2006;347:175–182.
185. O'Leary DR, Kuhn S, Kniss KL, *et al*. Birth outcomes following West Nile Virus infection of pregnant women in the United States: 2003–2004. *Pediatrics* 2006;117:e537–e545.
186. Chapa JB, Ahn JT, DiGiovanni LM, Ismail MA. West Niles encephalitis virus during pregnancy. *Obstet Gynecol* 2003;102:229–231.
187. Alpert SG, Fergerson J, Noël L-P. Intrauterine West Nile virus: ocular and systemic findings. *Am J Ophthalmol* 2003;136:733–735.
188. Price ME, Fisher-Hoch SP, Craven RB, McCormick JB. A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy. *BMJ* 1988;297:584–587.
189. Mupapa K, Mukundu W, Bwaka MA, *et al*. Ebola hemorrhagic fever and pregnancy. *J Infect Dis* 1999;179(Suppl. 1):S11–S12.
190. Barton LL, Peters CJ, Ksiazek TG. Lymphocytic choriomeningitis virus: an unrecognized teratogenic pathogen. *Emerg Infect Dis* 1995;1:152–153.
191. Bonthius DJ, Wright R, Tseng B, *et al*. Congenital lymphocytic choriomeningitis virus infection: spectrum of disease. *Ann Neurol* 2007;62:347–355.
192. Dhand A, Nadelman RB, Aguero-Rosenfeld M, Haddad FA, Stokes DP, Horowitz HW. Human granulocytic anaplasmosis during pregnancy: case series and literature review. *Clin Infect Dis* 2007;45:589–593.
193. Rouphael NG, O'Donnell JA, Bhatnagar J, *et al*. *Clostridium difficile*-associated diarrhea: an emerging threat to pregnant women. *Am J Obstet Gynecol.* 2008;198(635):e1–e6.
194. Garey KW, Jiang Z-D, Yadav Y, Mullins B, Wong K, DuPont HL. Peripartum *Clostridium difficile* infection: case series and review of the literature. *Am J Obstet Gynecol* 2008(199):332–337.
195. Hassett DE. Smallpox infections during pregnancy, lessons on pathogenesis from nonpregnant animal models of infection. *J Reprod Immunol* 2003(60):13–24.
196. Nishiura H. Smallpox during pregnancy and maternal outcomes. *Emerg Infect Dis* 2006;12:1119–1121.
197. Napolitano PG, Ryan MA, Grabenstein JD. Pregnancy discovered after smallpox vaccination: Is vaccinia immune globulin appropriate? *Am J Obstet Gynecol* 2004;191:1863–1867.
198. Ryan MA, Seward JFand the Smallpox Vaccine in Pregnancy Registry Team. Pregnancy, birth, and infant health outcomes from the National Smallpox Vaccine in Pregnancy Registry, 2003–2006. *Clin Infect Dis* 2008;46(Suppl. 3):S221–S226.