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5.16 Infections in Pregnancy☆

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Glossary

Arbovirus A group of viruses transmitted by arthropod vectors.
Congenital A condition present from birth.
Fetus Prenatal human between its embryonic state and its birth.
Low birth weight (LBW) A birth weight of a live born infant of less than 2500 g regardless of gestational age.
Microbiome/microbiota The ecological community of microorganisms that inhabit in or on our body.
Miscarriage Spontaneous loss of a pregnancy before the 20th week.
Neonate A newborn child.

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Preterm birth Babies born before 37 completed weeks of gestation.
Sepsis A life-threatening condition where a whole body inflammatory response is activated due to an infection.
Sequelae A pathological condition resulting from a prior disease or injury.
Stillbirth A baby born dead after 24 completed weeks of pregnancy.
TORCH An acronym for Toxoplasmosis, Other, Rubella, Cytomegalovirus (CMV), and Herpes infections that are some of the most common infections associated with congenital anomalies.
Vertical Transmission When an infection is transmitted directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth.

5.16.1 Introduction

In the 1940s, serious birth defects in infants born to women infected with rubella during their first trimester provided the first evidence that adverse pregnancy outcomes could result from maternal infection. It has become well recognized that infections during pregnancy, in addition to affecting the mother, may affect or be passed to the developing fetus. Infections are caused by bacteria, viruses, or parasites that have invaded body tissues or have released toxins disrupting normal functions and eliciting an inflammatory response to help combat the microorganism. Infections, or the inflammatory responses to an infection, can result in adverse effects including preterm delivery, birth defects, developmental delays, or stillbirths.

The main focus of this article is to explore the variety of pathogens that can lead to adverse effects to the fetus or neonate. There are various factors that can impact infection and susceptibility during pregnancy, some of these will be examined in detail, focusing on new data and information. Databases searched for this information included PubMed, Google Scholar, and Web of Science focusing on publications from 2007 to 2016. Since the publication of the previous Comprehensive Toxicology 2nd Edition, new sections included in this article discuss the transmission of intrauterine infections; the factors impacting infection; examples of classic and new pathogens capable of causing intrauterine infections; and an updated table of additional selected pathogens detailing the exposures, symptoms, and outcomes of infection.

5.16.2 Transmission

Bacteria, viruses, and other organisms are able to be passed from mother to child, a phenomenon known as transmission. The specific symptoms of transmitted infections depend on the individual pathogen and the stage of pregnancy at the time of infection. Transmission occurs in the womb during pregnancy or during birth. Pathogens can enter the uterus and infect the fetus through several routes—the most common routes are vertical transmission, such as hematogenous route where pathogens gain entry to the fetus by passing through the placenta, and ascending transmission, such as pathogens traveling up the reproductive tract of the pregnant woman. Other less common routes are passage from the abdominal cavity and through the fallopian tubes, invasive medical procedures, or the birthing process (Richardson et al., 2010). The main routes of intrauterine infection during pregnancy are vertical transmissions.

5.16.2.1 Vertical Transmission

A vertically transmitted infection is caused by a pathogen transmitted directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth; this type of transmission is also known as mother-to-child transmission. Vertical transmission during the perinatal period can be subcategorized as a perinatal infection.

Vertical transmission generally refers to transplacental transmission. The pathogen reaches the placenta through the mother's blood (hematogenous transmission). These pathogens must have the ability to overcome the placental barriers—syncytiotrophoblast interface, decidual–trophoblast interface, and physical obstacles (Robbins and Bakardjiev, 2012). Pathogens may overcome these barriers through a damaged syncytiotrophoblast interface; invasion of the uterine–trophoblast interface directly or cell-to-cell transport (e.g., *Listeria monocytogenes*); or immune cells may allow for barrier crossing (transport of human immunodeficiency virus mediated by leukocytes) (Robbins and Bakardjiev, 2012; Lagaye et al., 2001). When the placenta is infected, this may allow for the pathogen to invade the fetus.

5.16.2.2 Ascending Infection from Maternal Reproductive System

Ascending infections occur when infectious pathogens residing in the external genitalia of the mother access the amniotic sac. Upon infection, the amniotic sac may become compromised and rupture. Once ruptured, the pathogens may inoculate the amniotic fluid, spread as a biofilm over the exposed amnion, and invade choriodecidual tissue planes (Kim et al., 2009; Redline, 2012). The fetus

can become infected by aspirating the microorganism to the lungs, ingesting the pathogens, or by the pathogen penetrating the ear canal. See section on chorioamnionitis for details of post amniotic fluid infection.

5.16.3 Factors Impacting Infection

Susceptibility of infection in women differs due to natural variation; however, a number of other factors also influence this susceptibility. For intrauterine infections, there are some common factors that impact susceptibility to infection.

5.16.3.1 Immune System Changes During Pregnancy

Epidemiologic studies have shown that pregnant women have an increased incidence of contracting a variety of infections like influenza, varicella, measles, severe acute respiratory syndrome, tuberculosis, listeriosis, pneumocystis, toxoplasmosis, and malaria (Sappenfield et al., 2013; Riley et al., 2011; Jamieson et al., 2006). The severity of infection has been suggested to vary at different stages of pregnancy, likely from the unique immunological alterations that occur during different stages of pregnancy (Faucette et al., 2015).

To accommodate the genetic differences between the mother and the fetus and to prevent allogenic rejection of the fetus, the maternal immune system shifts toward a T-helper 2 bias (Jamieson et al., 2006). Maternal hormone levels change during pregnancy, and interplay between the sex hormones and immune system may alter the efficiency of the maternal immune system. These changes are thought to contribute to an increase in susceptibility toward certain infectious diseases which may change the severity of illness the mother experiences and fetal mortality rates.

Pregnant women may be considered immunosuppressed, though not in the traditional sense of the word. A fetus derives half of its genetic material from its father; thus, the fetus is essentially a foreign tissue in the maternal uterine environment. The fetus' susceptibility to rejection from its mother's immune system has been compared to an organ transplant (Jamieson et al., 2006). Evidence suggests that the maternal immune system tolerates fetal antigens by suppressing cell-mediated immunity while retaining normal humoral immunity and response (Jamieson et al., 2006). Though only occurring locally at the maternal–fetal interface, this suppression prevents the rejection of the fetal tissue and has been suggested that it may affect maternal response to infection (Jamieson et al., 2006; Erlebacher, 2013). The exact immunological tolerance is not completely understood.

During pregnancy, there is a systematic shift from T-helper 1 (Th1) to T-helper 2 (Th2) cell-mediated responses in the mother. In a Th1-dominated response, the Th1-type T lymphocytes and proinflammatory cytokines amplify cell-mediated immunity allowing for recognition of the body's own cells that engulf the pathogen and express pathogen-related antigens on their surfaces (Jamieson et al., 2006; Corr et al., 2007). When shifting to the Th2 cell-mediated response, the Th2-stimulating cytokines dominate and suppress the Th1 T cell responses locally allowing for adequate humoral immune response while the cell-mediated immunity is compromised (Thaxton and Sharma, 2010). Hormonal changes during pregnancy promote this shift from Th1 to Th2.

5.16.3.2 Hormones

Hormones can contribute to a modified immune response by altering the functions of immune cells and can have effects on the outcome of infection during pregnancy (Robinson and Klein, 2012). During pregnancy, steroid sex hormone levels change drastically and are considerably higher than at any other time during a woman's life, particularly pregnancy-associated hormones including estradiol, estriol, progesterone, corticosteroids, and prolactin (Robinson and Klein, 2012). The interplay between sex hormones and the immune system is complex and often contradictory—estradiol can enhance innate immunity in cell-mediated and humoral adaptive immune responses, yet progesterone can suppress the maternal immune response and alter helper T cell responses (Kourtis et al., 2014; Robinson and Klein, 2012). Research is needed to fully understand the changes in hormones and the immune system during pregnancy and the interplay between the two systems.

5.16.3.3 Stress

Pregnancy is a stressful change in a woman's body. Additional stressors beyond that of a pregnancy impact not only the health of the mother but also the development of the fetus. Stress can either enhance or suppress the immune system and thereby change the mother's susceptibility and severity to certain infections.

Mechanisms linking maternal stress to infant development are complex. Stressors can enhance or suppress immune function, which can change susceptibility to infections. The duration of stress impacts the health of the individual. Suppressed immunity can occur by decreasing immune cell number and function or increasing active immunosuppressive mechanisms. Maternal stress may be mediated through biological and behavioral mechanisms like the neuroendocrine pathway, which can result in the activation of the maternal–placental–fetal endocrine systems or an immune/inflammatory pathway, where maternal stress may modify the characteristics of systemic and local immunity by increasing susceptibility of the intrauterine and fetal environments to the immune inflammatory processes (Wadhwa et al., 2001). It is likely that the placenta plays a vital part in mechanisms linking maternal stress and infant development.

5.16.3.4 Microbiome

Traditionally, intrauterine infections were thought to have originated from pathogens in the vaginal tract that ascend into the intrauterine environment. The placenta was considered sterile during gestation and the presence of any bacteria in clinical cultures was a diagnostic for intrauterine infection (Hillier et al., 1988). However, the presence of placental or membrane bacteria has been observed in the absence of histological infection and recognition that the presence of bacteria does not always have the expected corresponding clinical outcomes when observed (Stout et al., 2013; Leviton et al., 2010; Han et al., 2009; Buhimschi et al., 2009; Steel et al., 2005; Mysorekar and Cao, 2014).

Of all the cells in the human body, only 10% are human somatic and germ cells; the remaining 90% are made of microflora (Savage, 1977). The microflora found in and on humans are composed of diverse niche communities of microbial species varying by site or organ. As a whole, all these communities make up the microbiome. With the initiatives set by the National Institutes of Health with the Human Microbiome Project in 2007, the microbiome has been found to be increasingly integral with the healthy functions of a human (Turnbaugh et al., 2007; Peterson et al., 2009).

Human–microflora interactions occur across body sites and have roles in metabolism, immunity, development, and behavior of the host (O'Hara and Shanahan, 2006; Cabreiro and Gems, 2013). The communities consist of a balance of commensal bacteria and beneficial bacteria that help humans with normal functions. When the balance is upset, it can result in disease and unfavorable alterations; under certain conditions, an outgrowth of potential pathogenic bacteria, a decrease in the number of beneficial bacteria, or an imbalance of commensal microflora may contribute to the pathogenesis of disorders which may affect the susceptibility rate for infections—including intrauterine infections (Round and Mazmanian, 2009; Hill and Artis, 2010; Honda and Littman, 2012; O'Hara and Shanahan, 2006). Infection with a pathogen leads to a change in the normal microbiome which can have an effect on the intrauterine system (Hacquard and Schadt, 2015). For instance, a decrease in the diversity in the placental microbiome has been correlated with lower birth weight in human infants (Zheng et al., 2015).

Many of the diverse groups of oral cavity bacteria have been found in the intrauterine environment and associated with adverse pregnancy outcomes suggesting that the oral cavity may act as a reservoir for infection (Mysorekar and Cao, 2014; Fardini et al., 2010; Han, 2011). These bacteria are capable of hematogenous transmission, similar to the transient bacteremia possible during periodontal infections (Fardini et al., 2010; Han, 2011; Offenbacher et al., 1999). For example, maternal oral infections, like acute gingival infection and chronic periodontal infections, are multifactorial disorders where microbial dental biofilms are considered the primary agent initiating inflammation (Chambrone et al., 2011; Offenbacher et al., 2006; Xiong et al., 2006). Although inflammation is typically restricted to local periodontal tissues, the pathogens can stimulate bacteremia and translocate to distant tissues (Champagne et al., 2000; Xiong et al., 2006).

Microorganisms have the ability to transfer from one location to another, as noted by studies on periodontal disease and its impact on pregnancy. As we continue to discover the complex roles and interactions between the human body and the microbiome that inhabits the body, it is likely that correlations between the health of the intrauterine microbiome and the susceptibility to intrauterine infection will be discovered.

5.16.4 Adverse Pregnancy Outcomes After Infection

Once infected, there are a multitude of adverse pregnancy outcomes—preterm births, chorioamnionitis, infections of the central nervous system (CNS), and sepsis—which are detailed in the following section (Richardson et al., 2010).

5.16.4.1 Preterm Births

Premature births, or preterm births, are defined as births that occur prior to 37 completed weeks of gestation, and they are associated with 5%–18% of pregnancies (Liu et al., 2012). Premature births are the leading cause of neonatal morbidity and mortality in the developed and developing world (Goldenberg et al., 2000). Infants who are born prematurely have a higher risk of serious disability or mortality than their full-term counterparts, with those infants born before the 30th week of pregnancy being especially at risk of prenatal mortality and morbidity. Potential problems for premature babies are an increased risk of short-term complications due to immaturity of organ systems, neurodevelopmental disorders, intellectual disabilities, vision/hearing impairments, or even death (CDC, 2015e; Romero et al., 2014).

Intrauterine infection is a frequent and important mechanism that may contribute to nearly 40% of preterm births (Goldenberg et al., 2008; Agrawal and Hirsch, 2012; Romero et al., 2007). However, this number may be higher because many infections are likely to be subclinical and the pathogenesis is not detected due to the lack of sensitivity of conventional culture techniques (Racicot et al., 2013). Outcomes of infection in a pregnant host are dependent upon various factors including gestational stage of fetus, previous exposure and immunity of the mother, variable immunity among individuals, the placenta's ability to protect the fetus from infection, and the developing immune system in the fetus (Richardson et al., 2010).

There are different pathways by which preterm birth from bacterial infection are known to occur. Two major events that are required for bacteria to induce preterm labor are (1) bacterial colonization in gestational tissues or the fetus and/or (2) bacterial counts reaching a threshold that elicits maternal immune inflammatory response that will induce preterm labor (Romero et al.,

2002; Richardson et al., 2010). Preterm labor is more frequent when a fetal inflammatory response is triggered as diagnosed by an increase in IL-1 and IL-6 and a decrease in IL-10 (Romero et al., 2007).

Compared to term infants, preterm births have a higher incidence rate of temperature instability, respiratory distress, apnoea, hypocalcaemia, seizures, jaundice, kernicterus, feeding difficulties, periventricular leukomalacia, and hospitalizations (Saigal and Doyle, 2008). Effects of preterm birth can manifest later in childhood (Huddy et al., 2001). Studies on low birth weight have shown that most of these infants showed sequelae like cognitive defects, academic underachievement, grade failures, and the need for increased remedial assistance during mid-childhood and adolescence continuing during life (Saigal and Doyle, 2008). There is still much about the pathogenesis and mechanisms of preterm birth that is not understood and animal models, such as sheep, have/are being utilized to gain knowledge that could lead to methods and treatments that can improve neonatal outcomes (Racicot et al., 2013; Goldenberg et al., 2008).

5.16.4.2 Chorioamnionitis

The condition in which the membranes that surround the fetus—the chorion and amnion, and the amniotic fluid—are infected by bacteria is commonly referred to as "chorioamnionitis." Chorioamnionitis complications are associated with significant and/or long-term adverse outcomes for the mother (postpartum infections and sepsis) and/or the infant (stillbirth, premature birth, neonatal sepsis, chronic lung disease, and brain injury) (Tita and Andrews, 2010). It has been estimated that one of every three preterm neonates is born to a mother with intraamniotic infection, identified with either cultivation or molecular microbiologic techniques (Berger et al., 2009). It is important to also note that microbial colonization of chorioamniotic membranes does not always result in a fetal or maternal inflammatory response (Romero et al., 2007). Chorioamnionitis is typically associated with bacteria that have low virulence and enter the uterus by ascending from the lower reproductive tract; it is rare that transmission is spread hematogenously (one notable exception: *Listeria monocytogenes*) (Richardson et al., 2010; Tita and Andrews, 2010). The presence of organisms in the amniotic cavity elicits an intense inflammatory response (Racicot et al., 2013). The inflammatory response may intensify and progress into fetal inflammatory response syndrome which predisposes preterm neonates to short- and long-term consequences (Goldenberg et al., 2008).

A maternal fever is an important criterion for the diagnosis of chorioamnionitis. The presence of maternal fever of greater than 38°C (100.4°F) and at least two of the following criteria: maternal leukocytosis (greater than 15,000 cells/mm^3), maternal tachycardia (greater than 100 beats/min), fetal tachycardia (greater than 160 beats/min), uterine tenderness, and/or foul odor of the amniotic fluid. These thresholds are associated with higher rates of neonatal and maternal morbidity (Polin and Committee on Fetus and Newborn, 2012).

Additional details of the mechanisms of chorioamnionitis can be found in Richardson, Pollak et al. (2010) and in Tita and Andrews (2010).

5.16.4.3 Infection of Fetal Central Nervous System

Adverse effects to the CNS is a common result of intrauterine infections in neonates. Transversal of the blood brain barrier (BBB) must occur for a pathogen to access the CNS (Polin and Harris, 2001). The BBB secretes cerebrospinal fluid (CSF) while physically separating the brain from the intravascular department. The purpose of the BBB is to control the flow of molecules and ions that enter and leave the brain in order to maintain a neutral environment (Kim, 2003; Richardson et al., 2010). The extent of effect depends on the maturity of the developing brain, timing of infection, or amount of pathogens (Kim, 2014).

5.16.4.3.1 Meningitis (bacterial)

There are an estimated six cases of bacterial meningitis per 100,000 people worldwide (NINDS/NIH, 2015b); however, there is little known about bacterial meningitis in the fetus (NINDS/NIH, 2015b). Generally, pregnancy has not been associated with an increased risk of bacterial meningitis with the exception if the cause is due to *Streptococcus pneumoniae*, *Listeria monocytogenes*, or *Cryptococcus neoformans* (Baldwin and Roos, 2011; Adriani et al., 2012). Clinical effects of meningitis are sepsis and increased intracranial pressure; chronic changes can occur such as hydrocephalus, encephalomalacia, or subdural effusion (Kim, 2014). Neonatal meningitis is the most common and serious bacterial infection during the neonatal period, with the most common pathogens being enterobacteria, *E.coli*, and group B streptococcus (Kim, 2014).

5.16.4.3.2 Hydrocephaly

Hydrocephaly is a condition where excess CSF accumulates in the brain: it is also known as hydrocephalus or "water on the brain" (NINDS/NIH, 2015a). The excessive accumulations cause an abnormal expansion of the brain's ventricles producing pressure on the brain (NINDS/NIH, 2015a). Due to the malleability of an infant's skull, the added pressure on the brain may result in an enlarged head size for the infant as the skull widens to relieve pressure (Richardson et al., 2010). Causes of hydrocephalus are still not well understood; possible causes in the fetus are infections, genetic defects, developmental disorders, meningitis, premature birth complications, or traumatic head injury (Richardson et al., 2010; NINDS/NIH, 2015a).

5.16.4.3.3 Microcephaly

Microcephaly is a medical condition present at birth or developed within the first few years of life wherein the circumference of the head is smaller than normal because the brain has either not developed properly or growth has stopped (NINDS/NIH, 2015c). It is

most often caused by genetic abnormalities during the early months of fetal development, but it may be induced if the mother is infected or affected by pathogens, drugs or alcohol, or certain toxic chemicals during pregnancy (NINDS/NIH, 2015c). Recently, pregnant women infected with the Zika virus had a high incidence of babies born with microcephaly. See sections Examples of Infection During Pregnancy, Viral Infections, and subsection Zika virus, for examples and a discussion.

The result of having microcephaly varies. Babies born with microcephaly will have smaller than normal heads that fail to grow through infancy. Microcephaly can be an isolated condition or occur in combination with other major birth defects (CDC, 2016b). Depending on the severity of microcephaly, problems can range from mild to severe and are often lifelong, such as impaired cognitive development, developmental delay, facial distortions, dwarfism or short stature, hyperactivity, seizures, difficulties with coordination and balance, feeding problems, hearing loss, vision problems, and other brain or neurological abnormalities (NINDS/NIH, 2015c; CDC, 2016b). Severe microcephaly can also be life-threatening (CDC, 2016b). Yet some will develop normally and their head will grow bigger especially if they are otherwise growing and developing normally (NINDS/NIH, 2015c).

5.16.4.3.4 Developmental delays

Infections during pregnancy may result in developmental delays for the infant. Pathogens that are able to interact with the CNS have capabilities of causing morbidities in fetuses and premature infants. Some of these impairments may not manifest at birth or in the neonatal period but later in life.

Many neonates are able to survive major insults, like infection, without any evidence of impairment due to the plasticity of the developing brain and improvements in medical care; yet, in others, these insults can cause varying degrees of long-term neurodevelopmental impairment such as cerebral palsy, with half of those continuing to develop cognitive and behavioral deficits (Mwaniki et al., 2012; Stoll et al., 2004).

The exact mechanisms whereby pathogens lead to developmental delays are not yet known. Molecular events such as the release of inflammatory cytokines by brain cells during infection may have a significant role in the brain injury (Dammann and Leviton, 1997). For instance, ascending intrauterine infections have been suggested to significantly increase the risk of fetal brain damage due to the initiation of fetal inflammatory response syndrome (Berger and Soder, 2015; Dammann and Leviton, 1997; de Vries, 2009). Yet, whether there are exposure-specific or pathogen-specific patterns by which cytokines act in response to inflammation during infection is unknown.

5.16.4.3.5 Sepsis

Sepsis is a systematic syndrome that occurs in response to infection of the blood and stems from an additional medical condition, like chorioamnionitis or a CNS infection (NIGMS/NIH, 2015). During sepsis, intravenous coagulation may occur, blocking blood flow to vital organs and creating hypoxic and ischemic conditions. Mortality in cases of sepsis is due to the failure of multiple organs—typically, a single organ fails leading to the dysfunction of other organ systems.

There is early and late onset of neonatal sepsis. Early onset is typically a consequence of fetal infection in utero or during parturition within the first week of life. Sepsis can begin in utero when the fetus inhales or swallows infected amniotic fluid; during parturition, sepsis is capable of developing within the hours or days after birth when colonized skin or mucosal surfaces are compromised (Polin and Committee on Fetus and Newborn, 2012). Maternal treatment with intrapartum intravenous antimicrobial agents is the only intervention proven to reduce the incidence of early-onset neonatal sepsis (CDC, 2010b; Polin and Committee on Fetus and Newborn, 2012). Late-onset sepsis can result from colonization during birth via vertical transmission of a colonized mother's anorectal and vaginal areas; case reports have suggested possible horizontal transmission in the postnatal period through breast milk (Berardi et al., 2013; Polin and Committee on Fetus and Newborn, 2012). Depending on the pathogen and the neonatologists' discretion, a full course of antimicrobials may be used to treat the neonate (Rubin et al., 2002). Vancomycin has been a frequent choice of empiric antimicrobial treatment of neonates with suspected late-onset sepsis (Rubin et al., 2002).

Chorioamnionitis is a major risk factor for neonatal sepsis and increased risk of early-onset sepsis (Polin and Committee on Fetus and Newborn, 2012; Wolfs et al., 2012). Additionally, pathogens associated with neonatal meningitis have the ability to induce neonatal sepsis. As mentioned previously, neonates that survive a CNS infection may experience developmental delays and impairment. A study showed that the degree of impairment was more likely to be severe in septic preterm neonates than in nonseptic neonates (Mwaniki et al., 2012).

5.16.5 Examples of Infection During Pregnancy

Infections that are acquired in utero or during birth are a significant cause of fetal and neonatal mortality which can contribute to early and later childhood morbidity. Organisms shown to cause these congenital conditions are included in the TORCH complex. The TORCH acronym represents *Toxoplasma gondii*, *O*ther infections, *R*ubella, *Cytomegalovirus*, and *H*erpes viruses as a concept emphasizing that these infections have been shown to cause stillbirths, perinatal morbidity, and 2%–3% of all congenital anomalies (Neu et al., 2015; Stegmann and Carey, 2002). These conditions are far from the only kinds that can cause congenital conditions. Specific examples of types of pathogens that affect pregnancy and the developing fetus are listed in **Table 1**. To explore some of the mechanisms unique to pathogens (bacterial, viral, parasitic, and fungal), a few examples are elaborated in this section.

Table 1 Effects of selected pathogens on fetuses and infants

Pathogen	*Exposure*	*Symptoms*	*Outcome of fetus/infant*	*Prevention*	*Sources*
Bacteria					
Brucella species	Contact with infected animals; consumption of contaminated raw milk or milk products; inhalation of aerosols; horizontal transmission; breast milk Most commonly reported laboratory-acquired infection	Fever, chills, sweating, weakness, malaise, headache, and joint and muscle pain	Spontaneous abortions	Avoid unpasteurized milk and unpasteurized milk products	Food and Drug Administration (2012), Kurdoglu et al. (2010)
Campylobacter jejuni	Raw milk, untreated water, raw and undercooked meat, poultry, or shellfish; vertical transmission	Diarrhea (sometimes bloody), stomach cramps, fever, muscle pain, headache, nausea, bacteremia, reactive arthritis	Intrauterine fetal infection, abortion, stillbirth, death in early life, enteritis, meningitis. Fetal harm increases when maternal bacteremia is present	Careful food preparation	Food and Drug Administration (2012), Smith (2002), Blaser (1997)
Clostridium perfringens	Meat and meat products, especially undercooked	Abdominal pain, diarrhea, occasional nausea and vomiting	Intravascular hemolysis, tissue necrosis, sepsis, fetal death	Careful food preparation	Food and Drug Administration (2012), Blaser (1997)
Coxiella burnetii (Q fever)	Inhalation of aerosolized bacteria from bodily fluids of infected host animals (including humans); unpasteurized milk and milk products or foods made with unpasteurized milk; tick bites	Fever; severe headaches; muscle aches; chills; heavy sweating; nausea, vomiting, or diarrhea; dry cough; and abdominal or chest pain; may be asymptomatic	Preterm birth, neonatal death	Avoid unpasteurized milk and unpasteurized milk products	Langley, et al. (2003), Food and Drug Administration (2012)
Listeria monocytogenes	Unpasteurized milk and milk products or foods made with unpasteurized milk, cheeses (particularly soft cheeses), ice cream, raw vegetables, raw poultry and meats, fermented raw-meat sausages, hot dogs and deli meats, raw/smoked fish and other seafood	In pregnant women, flu-like symptoms, fever, headache, fatigue, muscle aches, nausea, vomiting, diarrhea. Many times, woman is asymptomatic	Miscarriage, fetal death, stillbirths, bacteremia, meningitis	Avoid unpasteurized milk and unpasteurized milk products; careful food preparation	Food and Drug Administration (2012), Allerberger and Wagner (2010), CDC (2013c), Farber and Peterkin (1991)
Salmonella enteritidis	Raw/undercooked eggs, raw meat, poultry, seafood, raw milk, dairy products, produce	Diarrhea, fever, vomiting, headache, nausea, stomach cramps	Sepsis, fetal death	Careful food preparation	Roll et al. (1996), Food and Drug Administration (2012)
Viruses					
Coxsackie virus	Person-to-person through the fecal–oral route	Acute febrile illness, myocarditis, pericarditis, pleurodinia, exanthemas or enanthemas, hand, foot, and mouth disease, herpangina, acute hemorrhagic conjunctivitis, aseptic meningitis, encephalitis	Increased rate of insulin-dependent diabetes mellitus, severe respiratory failure, mental retardation, myocarditis, cardiac anomalies. Neonates may experience pneumonia, myocarditis, meningoencephalitis, and/or a severe maculopapular rash	Careful personal hygiene	Ornoy and Tenenbaum (2006), Bauer et al. (2002)

Cytomegalovirus (CMV)	Person-to-person through bodily fluids and vertical transmission to fetus	Mothers are generally asymptomatic	90%–95% of affected infants are symptom-free at birth. Mental retardation, microcephaly, sensorineural hearing loss, and chorioretinitis are common symptoms. Fetal infection is most likely if maternal infection occurs in the first half of pregnancy	Careful personal hygiene, avoid organ and tissue transplantation from CMV-positive donors, antiviral drugs	Stegmann and Carey (2002), Stern and Tucker (1973), Shlyakhov et al. (1998a), Gindes et al. (2008)
Echovirus	Perinatal mother-to-fetus/ infant	Rashes, diarrhea, respiratory infections, myositis, meningitis, encephalitis, pericarditis	Poor feeding, lethargy, jaundice, hepatic failure, seizures, apnea, and hemorrhaging	Avoid cesarean sections; delay delivery to allow for transmission of antibodies from mother transplacentally	Ornoy and Tenenbaum (2006), Modlin et al. (1981), Modlin (1980)
Hepatitis B	Horizontally by blood and sexual transmission. Vertically during pregnancy or labor	Loss of appetite, nausea, vomiting, fever, abdominal pain, jaundice	Low birth weight is common if infection occurs in the third trimester	Avoid contact with infected persons or blood	Borgia et al. (2012), CDC (2015f), Ornoy and Tenenbaum (2006)
Hepatitis C	Typically by blood. Rarely by sexual transmission. Low mother–fetus transmission	Information not available	There may be a greater risk of fetal complications; however, data are inconclusive	No vaccine. Avoid contact with those infected	CDC (2015f), Ornoy and Tenenbaum (2006)
Hepatitis E	Fecal–oral route; vertical transmission	Loss of appetite; nausea; abdominal pain; pain in joints; enlarged liver; jaundice; fever Pregnant women tend to get sicker and more likely to die; can cause hepatic damage and/or failure	Preterm deliveries, perinatal mortality and morbidity	Careful food preparation; careful personal hygiene	Food and Drug Administration (2012), CDC (2015f), Kumar et al. (2004)
Herpes simplex virus (herpes simplex)	Transmission from new HSV infections near delivery or reactivation of latent infection of prior maternal infection	Blistering and ulceration of external genitalia, fever or myalgia May also be asymptomatic	Abortion, stillbirths, congenital malformations, or severe neurodevelopmental disabilities	No vaccine Antiretroviral therapies (acyclovir and/or valaciclovir therapies)	Stegmann and Carey (2002), Shlyakhov et al. (1998b)
Human immunodeficiency virus (HIV)	Vertical transmission from pregnant women to fetus not only during the last trimester but also during delivery or breastfeeding	Blood specimen positive 48 h after birth	Fetus/infant becomes infected with the virus	Antiretroviral therapies (especially zidovudine and combination therapies)	Watts et al. (2003), Shlyakhov et al. (1998b), Sauerbrei and Wutzler (2007)
Influenza	Postnatal transmission, possibly vertical transmission	Mother with flu	Preterm birth, low birth weight	Vaccines are available	CDC (2015b), Mosby et al. (2011), Yates et al. (2010)
Measles (morbilli, rubeola, or red measles)	Person-to-person contact	Maternal rash, fever	Spontaneous abortion, premature labor, increased fetal/neonatal loss	Measles-mumps-rubella (MMR) vaccine, which has greatly reduced incidence in developed nations	Ornoy and Tenenbaum (2006), Chiba et al. (2003)
Rubella virus (German measles or three-day measles)	Vertical transmission from mother to placenta and fetus	Mother with rubella	Spontaneous abortion, stillbirth, damage to fetal organs, hearing loss, heart abnormalities, ocular defects, encephalopathy	Vaccination of children and female teenagers with MMR vaccine, which has greatly reduced incidence in developed nations	Stegmann and Carey (2002), Shlyakhov et al. (1998b)

(Continued)

Table 1 Effects of selected pathogens on fetuses and infants—cont'd

Pathogen	*Exposure*	*Symptoms*	*Outcome of fetus/infant*	*Prevention*	*Sources*
Varicella zoster virus (Chickenpox)	Contact with infected individuals	Chicken pox, shingles	Congenital limb hypoplasia, skin scarring, damage to the eyes and CNS	Chicken pox vaccine	Shlyakhov et al. (1998b)
Human parvovirus B19 (Fifth disease)	Vertical transmission to fetus	In children, slapped cheek rash	Hydrops fetalis, fetal death, acute arthritis	Avoid contact with infected individuals	Stegmann and Carey (2002), Shlyakhov et al. (1998b)
Zika virus	Likely by blood. Possibly by sexual transmission. Vertical transmission to fetus	Fever, rash, joint pain, conjunctivitis, muscle pain, and headache	Associated with microcephaly, Guillain–Barré Syndrome, and other neurological disorders	No vaccine available	Triunfol (2015), WHO (2016a,b), Higgs (2016), Foy et al. (2011), Schuler-Faccini et al. (2016)
Parasites					
Neospora caninum	Infected cats, dogs, cattle, and other animals	No occurrence has been found in humans. Zoonotic potential is unknown, but caution should still be taken	No occurrence has been found in humans. Zoonotic potential is unknown, but caution should still be taken	Use caution when disposing of pet waste (i.e., changing a litter box). Wash hands after dealing with animals	Quinn et al. (2002), Dubey and Lindsay (1996)
Plasmodium falciparum (Malaria)	Bites from female mosquitoes carrying infected blood	Maternal anemia	Low birth weight	Use preventative measures against mosquito bites (insect repellant, bed nets, etc.). Chloroquine chemoprophylaxis and sulfadoxine–pyrimethamine intermittent treatment	Bardaji et al. (2011), WHO (2015b), White et al. (2014)
Toxoplasma gondii	Uncooked meat, cats/cat feces	Typically asymptomatic. Fever, fatigue, muscle pain, sore throat, headache. Encephalitis may occur in immunocompromised patients	Hydrocephalus, ventricle dilation, blindness, mental retardation, intracranial calcification, or chorioretinitis	Avoid consuming raw or undercooked meat, unpasteurized goat's milk, and untreated water; wash hands well after handling cats, litter boxes, and soil; possibly raw shellfish; pregnant women should not handle cat feces	Food and Drug Administration (2012), Stegmann and Carey (2002)
Fungi					
Candida infection (thrush, vaginal yeast infection, invasive candidiasis)	Unhygienic practices in medical setting; imbalance on persons	Mother positive for *Candida* infection	Chorioamnionitis, preterm birth, low birth weight, congenital cutaneous candidiasis	Careful personal hygiene See healthcare provider; treatments available	CDC (2015a), Ito et al. (2013)

5.16.5.1 Bacterial Infection

5.16.5.1.1 *Listeria monocytogenes*

Listeriosis is predominantly a foodborne disease associated with the consumption of contaminated foods—primarily in dairy products. Populations most susceptible to *L. monocytogenes* infection are people with a compromised immune system, older people, pregnant women, and neonates. These populations account for at least 90% of reported infections (CDC, 2013a).

Pregnant women are about 10 times more susceptible to *L. monocytogenes* infection than healthy, nonpregnant adults; about one in seven (14%) cases of listeriosis occur during pregnancy (CDC, 2013a; 2013c). Infection during pregnancy can cause spontaneous preterm labor, fetal loss, and illness or death in newborn infants (CDC, 2013c; Richardson et al., 2010). Symptoms of infection may include gastrointestinal symptoms, influenza-like illness with fever, headache, myalgia, and/or backache, but 29% of the infection cases are asymptomatic (Mylonakis et al., 2002; Jackson et al., 2010).

Animal studies on rhesus monkeys (Smith et al., 2003), guinea pigs (Williams, 2006), and gerbils (Roulo et al., 2014) have shown a relationship between increasing bacterial load and adverse pregnancy outcomes. A fetus becomes infected when *L. monocytogenes* crosses the placenta, which has been suggested to be a reservoir for reinfection (Bakardjiev et al., 2006; De Luca et al., 2015). Neonatal infection occurs in 68% of the cases of maternal infection; 68% of the cases may make a full recovery, but in 12.7% of cases, there may be long-term sequelae (Mylonakis et al., 2002). Infection may lead to severe health conditions such as septicemia, pneumonia, or meningitis and in about 25% of cases, the occurrence of preterm delivery with birth weights lower than normal or stillbirth may occur (Mylonakis et al., 2002). Septicemia is the main symptom that neonates display with a 15%–50% mortality rate. Other symptoms include respiratory problems, pneumonia, and the formation of minute abscesses in bodily organs (Farber and Peterkin, 1991). A neonate can develop late-onset listeriosis through natural birth if the mother's vaginal tract has been colonized by *L. monocytogenes* (CDC, 2013c).

Bacteremia can be caused by ascending infection, transplacental passage of the organism, or by inhalation of amniotic fluid (Becroft et al., 1971; De Luca et al., 2015). Second- and third-trimester infections can result in premature delivery followed by neonatal illness or preterm delivery of a stillborn (Farber and Peterkin, 1991). For additional discussion of mechanisms, see Richardson, Pollak et al. (2010).

5.16.5.1.2 *Streptococcus*

Streptococcus are classified by their hemolytic properties with two species known to affect pregnancy—alpha-hemolytic streptococci (group A strep) and beta-hemolytic streptococci (group B strep). We will be detailing examples from group A strep and group B strep in the following section because of their potential impact on pregnancy.

A Group A streptococci, *Streptococcus pneumoniae* or pneumococcus, is a significant human bacterium. It is part of the normal microbiome in the upper respired tract, but opportunistic, if conditions allow. It is one of the most common causes of severe pneumonia and can cause pneumococcal meningitis, which is the most common form of meningitis and the most serious (NINDS/NIH, 2015b; CDC, 2015d). Coexisting disease in the mother increases the risk of contracting pneumonia in pregnancy.

A pregnancy complicated with pneumonia can have adverse fetal effects; 44% of women experienced preterm labor and of the preterm births, 36% had respiratory failure (Munn et al., 1999). Pneumonia in pregnancy can result in inflammation and edema of alveoli, restricting the number available for oxygen transport. Fetal oxygen delivery decreases when the maternal oxygen saturation falls to $<90\%$ (Goodnight, 2005). Birth weights were significantly lower at delivery during pregnancies complicated by pneumonia (Goodnight, 2005).

Invasive Group B *Streptococci* (Group B Strep) or *Streptococcus agalactiae* is the leading infectious cause of maternal chorioamnionitis, puerperal endometritis, and early-onset neonatal sepsis (Phares et al., 2008; CDC, 2010b). It causes invasive disease primarily in infants, pregnant/postpartum women, and older adults, with the highest incidence among young infants (Phares et al., 2008).

There are two main types of Group B Strep disease—early-onset disease and late-onset disease. Early-onset disease occurs during the first week of life and late-onset disease occurs from the first week through the first three months of life. During early-onset disease, Group B Strep commonly causes sepsis, pneumonia, and, sometimes, meningitis (CDC, 2014). For late-onset disease, the same illnesses are found as in the early onset, but meningitis is more common during this type of disease (CDC, 2014). The primary risk factor for neonatal infection transmission is colonization of the mother's genital tract through direct exposure during birth, or in fetuses through ascension into the amniotic fluid then into the placenta. Group B Strep can also cause miscarriages, stillbirths, and preterm deliveries (CDC, 2014). The exact mechanisms are generally unknown (CDC, 2014).

5.16.5.1.3 *Campylobacter*

Campylobacter are found ubiquitously in the environment and considered normal intestinal flora in most mammals and birds. The consumption of raw or undercooked poultry or crosscontamination of other foods is the most common source of campylobacteriosis in industrialized nations, responsible for more than 90% of all sporadic cases in humans (Dasti, 2010; Allos, 2001). More than 90% of all human *Campylobacter* infections are caused by *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli*, with increasing rates of infection reported during the summer months.

Infants are one of the two most infected populations, the second group are patients between 15 and 39 years (Dasti, 2010). *C. jejuni*, *Campylobacter fetus* (*C. fetus*), and other strains have caused stillbirths/abortions in pregnant women (Smith, 2002). *C. jejuni* and *C. fetus* are two strains known to cause illness in pregnant/postpartum women and their fetuses/newborn infants. Though most cases have no complications, enteritis caused by *C. jejuni* infection can result in stillbirth or premature labor

(Allos, 2001). Transmission of the pathogen to offspring can occur either transplacentally or through vaginal delivery (Smith, 2002; Richardson et al., 2010).

Additional details into the mechanisms of *Campylobacter* intrauterine infection and the impacts on the fetus—such as stillbirth—may be found in the second edition of Comprehensive Toxicology, volume 8, Intrauterine Infections (Richardson et al., 2010).

5.16.5.2 Viral Infections

Rubella was the first virus recognized to result in birth defects. There are a number of viruses that can adversely affect the developing fetus (**Table 1**). Viruses act through different mechanisms of action; there are some common features of viral infections that adversely affect pregnancy. Transmission occurs vertically from the mother to the fetus. If the placenta is not infected, the virus does not appear to spread to the fetus. Various factors influence the likelihood of the virus infecting the fetus such as infection state of the mother and gestational age of the fetus. Outcomes of viral infections are generally spontaneous abortion, stillbirth, prematurity, and organ pathogenesis. In the following section are provided examples of viruses, additional examples may be found in **Table 1**.

5.16.5.2.1 Cytomegalovirus

Cytomegalovirus (CMV) is a herpes virus that infects people of all ages. Once infected, the virus stays within a person's body for life. In the United States, it is estimated that 50%–80% of adults are infected with CMV by the age of 40 (CDC, 2010a). Most healthy children and adults infected with CMV exhibit no symptoms; those that do exhibit symptoms tend to be like other illnesses—fever, sore throat, fatigue, and swollen glands. CMV can cause serious disease in pregnant women and their babies, people who care for infants and children, and the immunocompromised. It is the most common viral infection in the developing fetus; approximately 1 in 150 children is born with congenital CMV infection.

Transmission of this virus is generally through direct contact with body fluids. CMV can be transmitted from a pregnant woman to her fetus during pregnancy by the virus crossing the placenta and infecting the fetus' blood.

Congenital CMV infection in developed countries occurs between 0.3% and 2.45% of all live births (Peckham, 1990; Alford et al., 1990; Bonalumi et al., 2011). Most infants born with congenital CMV infection (90%) appear healthy at birth and 80% of the healthy appearing infants never develop symptoms or disabilities. Health problems or disabilities may appear 2 or more years after birth or never (CDC, 2010a). Fetal damage from CMV infection can include growth retardation and CNS abnormalities (Kimberlin et al., 2003).

Additional details regarding the mechanisms of CMV may be found in the second edition of Comprehensive Toxicology, volume 8, Intrauterine Infections (Richardson et al., 2010).

5.16.5.2.2 Influenza

Influenza viruses are a group of RNA viruses and are the leading cause of serious wintertime respiratory morbidity worldwide. Studies about the effects of influenza-related illness during pregnancy have shown an impact on the health of pregnant women. Specific changes in a woman's immune system, heart, and lungs during pregnancy increase the susceptibility to severe illness, hospitalizations, and possibly death. There is an increased chance for serious problems for unborn babies, including premature labor and delivery (McNeil et al., 2011). There are three distinct genera of influenza viruses: A, B, and C. For this example, we will be looking at the outcomes specific to the subtype of influenza A—the 2009 H1N1 influenza A virus.

Women hospitalized with H1N1 infection were estimated to have a three times increased risk of delivering preterm (Yates et al., 2010). Emergency cesarean deliveries were frequently reported as urgent or emergent in one study regarding the 2009 H1N1 influenza (Haberg et al., 2013). The unusually high cesarean section delivery is a likely effect of deteriorating maternal condition that impacts the overall fetal status (Mendez-Figueroa et al., 2011). Infants of ill mothers can test positive for H1N1 influenza, but it is an unusual occurrence. This raises the possibility of vertical transmission, but additional studies are needed on the impacts of maternal infection with influenza on neonatal outcomes. Long-term follow-up studies on infants born to women with influenza infection should be performed to fully understand the impacts on overall outcomes when evaluating influenza in pregnancy. Vaccines are available and recommended to pregnant women; see Centers for Disease Control and Prevention (2015) for recommendations (CDC, 2015b).

5.16.5.2.3 Hepatitis

Hepatitis refers to the inflammation of the liver. Though inflammation can be caused by various means, most commonly it is due to a virus. There are five main types of hepatitis viruses—A, B, C, D, and E. Hepatitis A and E are generally caused by the intake of contaminated food or water; hepatitis B, C, and D typically occur as parenteral contact with infected bodily fluids. Although hepatitis E has a high vertical transmission rate (50%), there is still limited data on complications (Ornoy and Tenenbaum, 2006; Kumar et al., 2004). For this example, we concentrate on Hepatitis B due to the effects it can cause on the pregnancy, to the fetus, and potential teratogenic effects of drugs used to prevent infection.

Maternal hepatitis B virus (HBV) infection has not been shown to increase major congenital defects in offspring. Reports of a higher incidence of low birth weight and prematurity have been noted during acute infection compared to the general population

(Jonas, 2009). The higher incidence may be attributed to the changes in the maternal immune system contributing to a suppressed immune response against HBV.

A high frequency of HBV perinatal transmission occurs in up to 90% of infants born to women positive for HBV infection. HBV is able to cross the placental barrier but presumed to be the cause of a minority of infections for those mothers not immunized (Jonas, 2009). Transmission of the HBV can occur prenatally when the virus enters the placenta through maternal blood and crosses the placental barrier gaining access to the fetus or during birth when the newborn is exposed to infected cervical secretions. Increased likelihood of intrauterine transmission has been associated with the level of HBV DNA in the mother. Prevention of HBV transmission can be performed by identifying the hepatitis B surface antigen in pregnant women and providing hepatitis B immune globulin and hepatitis B vaccine to the infants within 12 h of birth (CDC, 2015f).

5.16.5.2.4 Zika virus

The virus was first identified in Africa in 1947 and was named after the Zika forest in Uganda, where it was first isolated (Dick, 1953). Zika virus is a single-stranded RNA virus spread to people when they are bitten by an infected *Aedes* species mosquito (arbovirus). It is related to other flaviviruses including dengue and chikungunya (Triunfol, 2016). Transmission is typically through exposure to infected blood but transmission can result from vertical transmission from a pregnant woman to her fetus, sexual transmission, laboratory exposure, and potentially through blood and organ transplant (Musso et al., 2015; Foy et al., 2011; CDC, 2016a).

Many Zika infections are asymptomatic; common symptoms of Zika are fever, rash, joint pain, conjunctivitis, muscle pain, and headache which may appear 3–7 days after infection, last several days to a week, and are generally mild (CDC, 2015g; Schuler-Faccini and Rasmussen, 2016). Severe disease is uncommon; fatalities are rare (CDC, 2015g); however, Guillain–Barre syndrome has been reported in patients following suspected Zika virus infection (Oehler et al., 2014). The virus usually remains in the blood of an infected person for a week and can persist longer in other secretions such as semen. Once a person has been infected, they are likely to be protected from future infections (Rasmussen et al., 2016; Schuler-Faccini and Rasmussen, 2016).

The Centers for Disease Prevention and Control (CDC) acknowledges the link between Zika virus infection in pregnant women and subsequent birth defects—spontaneous abortion and fetal demise (Rasmussen et al., 2016; Schuler-Faccini and Rasmussen, 2016). A pregnant woman already infected with Zika can pass the virus to her fetus during pregnancy or around the time of birth (Rasmussen et al., 2016). Brain defects linked with Zika in the fetus include decreased total brain tissue with resulting microcephaly, calcium deposits in the brain indicating brain damage, excess fluid in the brain cavities and surrounding the brain, absent or poorly formed brain structures, and abnormal eye development (Rasmussen et al., 2016; CDC, 2016b; Schuler-Faccini and Rasmussen, 2016).

Zika can be sexually transmitted and can be passed from an infected partner before their symptoms start, while they exhibit symptoms, and after their symptoms end (WHO, 2016a; Schuler-Faccini and Rasmussen, 2016). The Zika virus can remain in semen (2–10 weeks) longer than in any other body fluids, including vaginal fluids, urine, and blood (Foy et al., 2011; Higgs, 2016; Oster, 2016; Musso et al., 2015).

Brazil's Ministry of health made an announcement as of December 2015 for "…women in the northeast of the country not to get pregnant for the foreseeable future" (NPR, 2015). In Jan. 2016, the CDC issued a travel notice Alert level 2 regarding the Zika virus in South America, Central America, Mexico, the Caribbean, and Puerto Rico. The World Health Organization has declared a Public Health Emergency of International Concern on Feb. 1, 2016 (WHO, 2016b). Since 2015, 71 countries and territories reported evidence of vector-borne Zika virus transmission (WHO, 2016a). As of summer 2016, the United States reported 43 locally acquired mosquito-borne cases all from the state of Florida (CDC, 2016a).

5.16.5.3 Parasitic Infections

Parasitic infections affect pregnant women worldwide and directly or indirectly lead to a variety of adverse fetal effects. These effects include intrauterine retardation of growth, congenital malformations, and fetal loss. Depending on when the infection takes place and the stage of pregnancy the fetus is in, severe fetal consequences may occur during development or be asymptomatic until later in the pregnancy.

5.16.5.3.1 Malaria

Malaria is a protozoan disease transmitted by female mosquitoes of the genus *Anopheles*. The parasites multiply in the host's liver and subsequently infect the red blood cells causing symptoms of fever, headache, and vomiting; if not treated, the infection can become life-threatening by disrupting the blood supply to vital organs. In 2015, there were an estimated 214 million malaria cases and 43,800 malaria deaths; young children, pregnant women, and those nonimmune travelers are the most at risk when infected (WHO, 2014). In areas with high transmission rates, more than 70% of malaria deaths occur in the age group of children under the age of five (WHO, 2015b).

Pregnant women have increased susceptibility to *P. falciparum* malaria. Malaria during pregnancy increases the risk of maternal and fetal anemia, stillbirth, spontaneous abortion, low birth weight, and neonatal death (WHO, 2015a). The effects of low birth weight have an odds ratio of two to seven times higher effects when it is the woman's first pregnancy compared to women who have had multiple pregnancies prior (Desai et al., 2007; White et al., 2014). In malaria-endemic countries, pregnant women are at increased risk of developing severe *P. falciparum* malaria with a very high mortality rate, approximately 50% (White et al.,

2014). Maternal HIV infection also predisposes pregnant women to malaria, congenital malaria, and exacerbates reductions in birth weight (Steketee et al., 2001).

The risk of infant death is high if maternal malaria occurs late in pregnancy (Bardaji et al., 2011; White et al., 2014). Congenital malaria occurs in roughly 5% of neonates but clears spontaneously in 62% of cases (Falade et al., 2007). The condition is typically defined as the presence of asexual forms of malaria parasites in the peripheral blood within the first 7 days of life but frequently reported with the presence of the parasites in cord blood (Menendez and Mayor, 2007). *P. falciparum* contributes to 8%–14% of low birth weight deliveries (White et al., 2014).

With increased malaria prevention (early diagnosis and treatment) and control measures, the malaria mortality rates have fallen globally among all age groups. There is, however, a concern of *P. falciparum* resistance in some countries to artemisinin, one of the core compounds in World Health Organization recommended treatments for uncomplicated malaria (WHO, 2015b).

5.16.5.3.2 Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii* (*T. gondii*) that infects most species of warm-blooded animals. It has a complex life cycle. Sexual reproduction can only occur in the digestive tract of Felidae hosts (cats). Asexual reproduction can occur in any warm-blooded vertebrate. Humans can be infected by eating undercooked meat of animals harboring tissue cysts, consuming contaminated food or drinking water, contact with contaminated environmental samples, blood transfusion or organ transplant, or by vertical transmission. In humans, those infected are generally asymptomatic; when symptoms occur, it is usually mild and flu-like lasting for weeks to months and until the cycle returns to a dormant state (CDC, 2013b). The parasites form tissue cysts and may remain throughout the life of the host (CDC, 2013b).

If a woman has contracted toxoplasmosis before becoming pregnant, the fetus will be protected due to the mother's developed immunity (Woudwyk et al., 2012). So maternal–fetal transmission only occurs when a pregnant woman is newly infected with *Toxoplasma*. Global estimates of maternal–fetal transmission are approximately 20%–33% of newly infected pregnant women (Carlier et al., 2012). Although transmission rates during the first trimester of pregnancy are low (below 6%), when it does occur the damage to the fetus is the most severe at this time (Carlier et al., 2012). The second and third trimesters' transmission rates increase to 22%–40% and 58%–72%, respectively; the highest proportions of transmission occur in the last few weeks before birth (Carlier et al., 2012).

Transmission may result in a miscarriage, stillbirth, or a child with congenital toxoplasmosis. Infants infected before birth may be asymptomatic at first but may develop later in life with potential vision impairment/loss, mental disability, and seizures (CDC, 2013b). Treatment is available for pregnant women, newborns, and infants involving sulphonamides or spiramycin, but due to the parasites residing within cells in a less active phase, it is difficult for medication to completely eliminate the cysts (Richardson et al., 2010; CDC, 2013b).

5.16.5.4 Fungal Infections

Fungi are ubiquitous, found outdoors, on many inside surfaces, and on human skin. Most fungi are harmless, but some types can be harmful to health. Anyone can be affected by fungal diseases (CDC, 2015c). Serious fungal infections are uncommon during pregnancy; in some cases, infection may occur with higher frequency during pregnancy, potentially increasing maternal mortality and cause fetal loss or prematurity (Ostrosky-Zeichner and Rex, 2010). An extreme outcome of a fungal infection is the spread of the fungus through the blood to the spinal cord leading to fungal meningitis.

5.16.5.4.1 Candida

Candida is a genus of yeasts and is the most common cause of infections worldwide (Manolakaki et al., 2010). There are over 150 species. Many of the species are harmless commensals or endosymbionts under normal conditions; when conditions are sufficient, they can invade and cause disease. *Candida albicans* (*C. albicans*) and *Candida parapsilosis* (*C. parapsilosis*) are the two most likely species to cause candidiasis and candidemia.

Up to 40% of pregnant women may have vaginal colonization with *Candida* spp. (Goldenberg et al., 2000; DiGiulio, 2012). *Candida* spp. have been isolated from amniotic fluid of spontaneous preterm birth mothers (Maneenil et al., 2015). Cases studied have shown intraamniotic infection can cause fetal death or fetal candidiasis with impaired CNS outcomes in humans (Marelli et al., 1996; Benjamin et al., 2006; Darmstadt et al., 2000; Siriratsivawong et al., 2014).

In neonatal candidiasis, *C. albicans* and *C. parapsilosis* are the most commonly isolated species and cause the majority of fungal infections in very low birth weight infants. Though *C. albicans* is not specifically associated with the risk of preterm delivery, there has been some evidence that suggests the elimination of the yeast reduces the risk of a late miscarriage and preterm birth (Maneenil et al., 2015). *C. albicans* is usually vertically transmitted, whereas *C. parapsilosis* is mostly transmitted by contact other than parent–child (Waggoner-Fountain et al., 1996; Reef et al., 1998; Chapman and Faix, 2000; Abi-Said et al., 1997). Pathogenesis likely involves ascension of the infection from maternal *Candida* infection then leading to amniotic fluid infection and chorioamnionitis/funisitis (Siriratsivawong et al., 2014).

Approximately 9%–10% of nosocomial blood infections in neonates are fungal infections; 85.6% of these infections are caused by *Candida* spp. (Blaszkowska and Goralska, 2014). The mortality rate is the second highest ranging from 40% to 70% (Blaszkowska and Goralska, 2014). At risk neonates can develop candidiasis, a dermatitis caused by *Candida* spp. The dermatitis usually resolves on its own in neonates born full-term; however, the condition may advance to candidemia in very low birth weight infants possibly

leading to death. Some of the risk factors for dermatitis are vaginal birth, extreme prematurity, low birth weight, hyperglycemia, and steroid administration.

Congenital cutaneous candidiasis can present in a variety of symptoms—diffuse skin eruption in the absence of systemic illness to severe systemic disease leading to stillbirth or early neonatal death (Darmstadt et al., 2000). Cutaneous eruptions occur in 82% of cases and are typically detected within 24 h of birth (Darmstadt et al., 2000). Diagnosis of congenital candidiasis may be delayed due to the similar appearance to more common rashes in newborns which increases risk for adverse sequelae (Siriratsivawong et al., 2014).

Adhesion is a major virulence factor for this fungus. *Candida* spp. has the capability of forming biofilm which allows it to adhere to skin, mucus layers, and surfaces of tubes/catheters that may be used on neonates during hospitalization. There is evidence that *Candida* spp. has the ability to form biofilms on intrauterine devices (IUD). Due to IUD application directly affecting the vaginal ecosystem, there may be a need for the consideration of *Candida* spp. internal exposure for those women planning to get pregnant after removing the IUD (Caliskan et al., 2011).

5.16.6 Conclusion

Since the 1940s' outbreak of rubella, it has become well recognized that infections during pregnancy can affect the mother and fetus. For most women, pregnancy is a normal and healthy state. But there are factors that may make pregnant women more susceptible to infection. Changes in the immune system and the altering effects of hormones affect the immune system's susceptibility and responses to infection. Stress is common during pregnancy, but high levels may increase the risk of certain problems with delivering a healthy neonate by influencing the already altered immune functions. The diversity in the human microbiome has been correlated with the health of humans; as we learn more about the interconnecting relations between the microbiome and our health, promoting specific diversity may be able to protect the mother and fetus during pregnancy in the future.

Infection has long been established as the leading cause of preterm births which has its own risks such as the infection of the CNS or low birth weight, which can allow the neonate to be more susceptible to infections postpartum. Chorioamnionitis indicates infection of the intrauterine environment and is a major risk factor for neonatal sepsis, which can cause those neonates to commonly present with multiple insults or lead to a stillbirth. Stillbirths are an end to a pregnancy when the conditions in the mother are unable to keep the fetus alive.

Intrauterine infections are a diverse group of organisms that can cause a range of adverse outcomes in pregnancy. The TORCH complex is a reminder of organisms that can produce congenital defects when a woman is infected during pregnancy. The mechanisms of some infections are currently unknown and additional research is needed to understand how these pathogens cause adverse outcomes in pregnancy. Those that are understood may be preventable; others, like the Zika virus, are emerging and are only now being studied as outbreaks occur.

With the ever globalizing world, the risk of being exposed or contracting these infections rises as organisms can travel across continents in mere hours. Environmental factors such as changes in climate may allow for some organisms to move into more populated areas, exposing more individuals.

The understanding of intrauterine infections is vital to ensure the health of all future mothers and their offspring. Many factors influence the susceptibility of becoming infected. Contracting an intrauterine infection has health impacts on the mother and fetus. The fetus's development is a major concern after being exposed to an intrauterine infection but predicting the outcome for any individual is difficult with our current knowledge. There are many known organisms that are capable of producing congenital defects during pregnancy. However, there are new emerging organisms that have yet to be studied. Additional research to understand the mechanisms and risks associated with these organisms is critical for the health of all potential mothers and their offspring.

See also: 5.06. Maternally Mediated Developmental Toxicity. 5.08. Epigenetics and the Developmental Origins of Health and Disease.

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http://www.ninds.nih.gov/—National Institute of Neurological Disorders and Stroke—National Institutes of Health.
http://www.npr.org/—NPR: National Public Radio.
http://www.who.int/en/—World Health Organization: WHO.